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THERAPEUTICS:

ITS

PRINCIPLES AND PRACTICE.

BY

HORATIO C. WOOD, M.D., LL.D. (Lafayette Yale),

PROFESSOR OF MATERIA MEDICA AND THERAPEUTICS, AND CLINICAL PROFESSOR OF DISEASES OF THE NERVOUS SYSTEM, IN THE UNIVERSITY OF PENNSYLVANIA; MEMBER OF THE NATIONAL ACADEMY OF SCIENCES.

ELEVENTH EDITION.

REMODELLED AND IN GREATER PART REWRITTEN.

HORATIO C. WOOD,

HORATIO C. WOOD, JR.,

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TO

DR. GEORGE B. WOOD, LL.D.,

THIS BOOK

IS DEDICATED BY THE AUTHOR, HIS NEPHEW,

AS A TOKEN OF RESPECT AND

AFFECTION.

PREFACE TO THE ELEVENTH EDITION.

IT is just a quarter of a century since, led by the feeling that the time had come when the study of Therapeutics could, with a fair hope of success, be approached from the scientific point of view, I published the first edition of the present treatise. The result has far exceeded my most sanguine expectations. The book was, I believe, the first in any language, certainly the first in the English language, to avowedly attempt to make the physiological study of drugs the chief basis of practical therapeutic teaching. Not only has it passed through ten large editions, but at present almost every work that is written on Therapeutics is upon a foundation of physiological study.

During these twenty-five years, always impressed by a sense of gratitude to the profession both in this country and abroad for the kind reception given to the book, I have endeavored by honest labor and studious attempt at fairness of consideration to make the work, so far as was in my power, worthy of the support which it has received. During the last ten years my time has been so occupied with public and private clinical duties that but little opportunity has been afforded for that personal work in the physiological laboratory which is necessary for the preservation of originality and freshness in the writings of the pharmacologist. For this and other evident reasons I have associated with myself my son, Dr. Horatio C. Wood, Jr., in the revision of this treatise. Together we have carefully gone over the whole subject; the result of our co-labors being the present volume, which on examination will be found to retain many of the old features, but to be, on the whole, so different from its predecessors as properly to be considered a new book.

Other editions have been chiefly improved by the interstitial incorporation of new matter; in the present edition an effort has been made throughout to get a new view of the whole subject of Therapeutics, and to present it in the most attractive form to the student as well as to the practitioner of medicine.

The principal changes in the work consist in making the various articles more closely conform to a uniform, carefully-thought-out plan of presentation; in putting in small type the descriptions of the general effects produced by drugs in the lower animals, minor discussions, and other matters of less importance than those considered in the general

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text; in cutting out certain discussions which were necessary in the earlier editions of the book, but have lost value at this time because of the general uniformity of professional opinion that has been reached in regard to their conclusions; in very carefully considering the language so as to obtain as great conciseness as is compatible with clearness; in taking the references out of the body of the text and putting them in nonpareil type at the end of the various chapters; in the addition of articles on a number of new drugs; and in the insertion of the approximate metric equivalents of apothecaries' weights and measures used in giving the doses. So much space has been saved that it has been found possible to lessen the size of the book without rendering it less thorough and complete; and I believe that the treatise has been made to represent the contemporary knowledge of physiological therapeutics more clearly and satisfactorily than it ever did before.

H. C. W.

UNIVERSITY OF PENNSYLVANIA, May, 1900.

PREFACE TO THE FIRST EDITION.

AT the present time, when the shelves of private and public libraries are groaning beneath their ever-increasing loads, when a thousand presses in every city send forth day and night their printed messages until the earth is filled with them, it seems almost presumptuous for any one to offer new volumes to the world. Indeed, art is so long, life is so short, that every student has the right to demand of an author by what authority he doeth these things, and to challenge every memoir for its *raison d'être*. This being so, it assuredly will not appear egotistical for the author to state that his voluntary task was first suggested by his own wants, and that to its performance he has brought the training, labor, and experience of years spent in the laboratory, the study, the class-room, and the hospital ward.

There are a number of excellent treatises upon materia medica and therapeutics ; yet in various attempts at original research, as well as in the ward and the lecture-room of the hospital, I have keenly felt the want of something more. There are many points of view from which a subject can be looked at ; there are many paths by which it may be approached ; and to me, other points of view, other modes of approach, have been far more enticing than those adopted in our standard treatises.

The old and tried method in therapeutics is that of empiricism, or, if the term sounds harsh, of clinical experience. As stated by one of its most ardent supporters, the best possible development of this plan of investigation is to be found in a close and careful analysis of cases before and after the administration of a remedy, and, if the results be favorable, the continued use of the drug in similar cases. It is evident that this is not a new path, but a highway already worn with the eager but weary feet of the profession for two thousand years.

That very much has been thus accomplished it were folly to deny. Leaving out of sight the growth of the last two decades, almost all of the current therapeutic knowledge has been gained in this way.

Therapeutics developed in this manner cannot, however, rest upon a secure foundation. What to-day is believed is to-morrow to be cast aside, certainly has been the law of advancement, and seemingly must continue to be so. What has clinical therapeutics established permanently and indisputably? Scarcely anything beyond the primary facts

that quinia will arrest an intermittent, that salts will purge, and that opium will quiet pain and lull to sleep.

To established therapeutic facts the profession clings as with the heart and hand of one man,—clings with a desperation and unanimity whose intensity is the measure of the unsatisfied desire for something fixed. Yet with what a Babel of discordant voices does it celebrâte its two thousand years of experience!

This is so well known that it seems superfluous to cite examples of the therapeutic discord; and one only shall be mentioned,—namely, rheumatism. In this disease, bleeding, nitrate of potassium, quinine, mercurials, flying blisters, purgation, opium, the bromides, veratria, and a host of other remedies, all have their advocates clamorous for a hearing; and above all the tumult are to be heard the trumpet-tones of a Chambers, "Wrap your patients in blankets and let them alone."

Experience is said to be the mother of wisdom. Verily she has been in medicine rather a blind leader of the blind; and the history of medical progress is a history of men groping in the darkness, finding seeming gems of truth one after another, only in a few minutes to cast each back to the vast heap of forgotten baubles that in their day had also been mistaken for verities. In the past, there is scarcely a conceivable absurdity that men have not tested by experience and for a time found to be the thing desired; in the present, homœopathy and other similar delusions are eagerly embraced and honestly believed in by men who rest their faith upon experience.

Narrowing our gaze to the regular profession and to a few decades, what do we see? Experience teaching that not to bleed a man suffering from pneumonia is to consign him to an unopened grave, and experience teaching that to bleed a man suffering from pneumonia is to consign him to a grave never opened by nature. Looking at the revolutions and contradictions of the past,—listening to the therapeutic Babel of the present,—is it a wonder that men should take refuge in nihilism, and, like the lotos-eaters, dream that all alike is folly,—that rest and quiet and calm are the only human fruition?

Since the profession has toiled so long and found so little, if further progress is to be made we must question the old methods and search out new ones, which haply may lead to more fruitful fields. In the ordinary affairs and business of life, when anything is to be accomplished, the effort always is to discover what is to be done, and then what are the means at command. A primary knowledge of the end to be accomplished, and a secondary acquaintance with the instruments, are a necessity for successful human effort; and until the sway of this law is acknowledged by physicians, medicine can never rise from the position of an empirical art to the dignity of applied science. Until within a comparatively recent period, it has been impossible to comply with this law. But, through the advances made by the pathologists and

by the students of the natural history of disease, we are fast learning the methods in which nature brings the body back to health. When this is done,—when disease is thoroughly understood,—we shall have wrought out the first element of the problem, shall have complied with the first requirement of the law.

It is scarcely within the province of a therapeutist, and certainly is not possible within the scope and limits of this work, to discuss at length the natural history of disease ; but it is allowable to point out evident indications for relief ; and this I have done to a greater or less extent throughout the book.

The work of the therapeutist is chiefly with the second portion of the law. Evidently, it is his especial province to find out what are the means at command, what the individual drugs in use do when put into a human system. It is seemingly self-evident that the physiological action of a remedy can never be made out by a study of its use in disease. Under all circumstances, the problem is one of the most complex with which the human mind has to grapple ; and to introduce into this problem the new and ever-varying factors of the effect of disease and its natural vibrations on the system is to put the matter beyond human prescience.

In spite, then, of Dr. Niemeyer's assertion that experiments made with medicaments upon the lower animals or upon healthy human beings have, as yet, been of no direct service to our means of treating disease, and that a continuation of such experiments gives no prospect of such service, it is certain that in these experiments is the only rational scientific groundwork for the treatment of disease. We must discover what influence a drug exerts when put into the body of a patient before we can use it rationally ; and we can gain this coveted knowledge only in the method indicated.

It has been strenuously objected, especially to experiments upon animals, that drugs do not act upon the lower creatures in the same manner as they do upon man. When I first commenced the studies whose outcome is the present volume, I was profoundly impressed with the truth of this oft-repeated assertion and with the difficulties which it put in the way. To-day I do not believe that, stated in its broad sense, it is true. Indeed, more strongly, I assert that it is not true ; that, in the vast majority of cases, the actions of drugs upon man and upon the lower animals are, though seemingly different, in reality similar ; that the more knowledge we acquire the fewer exceptions remain unexplained ; and that the whole matter is in all probability subject to laws whose development will greatly aid in our explanation of various obscure clinical phenomena.

The general proofs of these assertions are sufficiently obvious, I think, in the following pages to render it unnecessary for me to dwell upon them at length here : moreover, if they be not so obvious to others as to myself, space is here wanting for a full discussion of the subject.

I can only make a few general remarks, and point out some of what I believe to be the governing laws.

In the first place, degree and quality are distinct things, and should not be confounded. Yet they frequently are ; and because it requires as much morphia to kill a pigeon of a pound weight as to destroy a man, we are told that medicines act differently upon man and the lower animals. Evidently the conclusion is a *non sequitur*, and difference of susceptibility is no proof of difference in the mode of impression. A teaspoonful of Epsom salt may purge one man, while it may require ounces to affect another. Evidently there is a difference of susceptibility ; but when the impression is once made it is of the same character in each case. As with man and man, so with man and the pigeon,—susceptibility is no measure or gauge of the character of the impression.

A large number of drugs—indeed, it may be said, the larger number of important drugs—exert in the system antagonistic actions. Thus, atropia stimulates the spinal cord, but destroys the conducting power of the nerve-trunks. It is evident that as one or other of these influences predominates, will there be convulsions or paralysis. Now, if for any reason one animal be exceedingly sensitive to the spinal action of atropia, that animal will in belladonna-poisoning suffer from convulsions, while its fellow, which is affected chiefly by the nerve-action of the drug, will, under like circumstances, have paralysis. Here the mere clinician, with his superficial knowledge, seeing the paralyzed and the convulsed lying side by side, says, What a hopeless muddle ! Poor fools, these vivisectors ! they will never come to any good ! In truth, the differences in symptoms in these and in many other cases simply depend upon differences in susceptibility ; and the only lesson that the circumstance teaches is the importance of discovering the laws which govern these susceptibilities.

A law which governs the susceptibility to the action of drugs is, that the more highly specialized any system is the more readily affected is it by a medicine. Thus, the cerebrum of a man is far more highly organized than that of any other animal, and consequently he is far more sensitive to the action of drugs which affect the cerebrum than are the lower forms. Again, in the frog the spinal system is especially developed,—probably, in proportion to the cerebrum, more so than in any other of the animals commonly experimented with : consequently the batrachian is excessively sensitive to remedies which, like strychnia, affect the spinal cord. In obedience to this law, we have resulting the action of opium, —an action which has been considered the strongest proof of the hopelessness of any attempt to explain the effects of drugs upon a man by experiments upon the lower animals. In man, opium causes deep stupor and general relaxation ; in the frog, it causes tetanic convulsions. The explanation of these seeming inconsistencies is, however, very evident when the whole subject is looked at. Opium in all animals has a double action, one upon the cerebrum and one upon the spinal centres. In the

frog, the latter being the more highly organized, the spinal action overcomes the cerebral; in man, the cerebrum being the more sensitive, stupor replaces the convulsions: yet in man convulsions sometimes occur in opium-poisoning, and in the frog the dose can be so managed as to cause stupor.

A second law which seems to hold sway over the action of drugs upon different animals is that great differences of function in a system affect its relation to drugs: thus, in an herbivorous animal the alimentary canal is very different from what it is in the carnivora, whose digestive organs in turn differ from those of man,—the omnivore. Medicines which act upon the alimentary canal are apt to vary in their effects upon different orders of animals.

Converse to the above law is that which renders systems which are little specialized similarly acted upon by drugs in different classes of animals.

Thus, the general structure and the functions of the circulatory system are very uniform among vertebrates, as is also the action of those drugs which affect chiefly the circulation: thus, aconite, or digitalis, or potash, influences in the one way the heart of the frog, of the rabbit, and of man.

There are a very few apparent exceptions to the uniformity of the action of drugs upon all animals which seemingly contravene the laws that have been mentioned. These exceptions are so few, however, that without doubt advancing knowledge will by and by explain them all and show what are the laws which for the time being hold in abeyance or overcome those already stated.

An asserted fact which has recently been brought forward as revealing the worthlessness of animal experimentation is that some monkeys are not susceptible to the action of strychnia, while others are. Granting the truth of the asserted fact, it certainly is explainable. It is at least conceivable that a given species of animal may, by the gradually acquired habit of feeding upon a substance containing a narcotic poison, acquire an insusceptibility to the influence of that poison which shall as it were belong to its specific type, or, in other words, be an acquired specific character. The nervous system of the opium-eater becomes accustomed to the stimulant, and it is not impossible that a measure of the habit should be transmitted. If the Darwinian law of the gradual evolution by the survival of the fittest have any force, these curious apparent freaks of medicines in regard to their physiological action may be the result of this law, especially since it is species which are affected. It is not all monkeys that are proof against strychnia, but, as we are distinctly told, only one species of monkey; and, so far as I know, it is not all deer that are said to thrive when fed upon tobacco, but only the Virginia deer. Whether this conception be or be not a mere fancy, this much is to my mind very clear, that the few scattered exceptions ought not to outweigh the immense mass of evidence upon the

other side, and that it is inconceivable that drugs, in their relations to animal organisms, differ from all other created things in not being subject to law.

In the early portion of this preface I stated that the work had grown out of a need felt by myself: that need was for a book into which should be gathered the many scattered facts in regard to the physiological action of medicine,—a book in which an attempt should be made to sift the true from the false, to reconcile seeming differences, to point out what we know and what we do not know, and to give a platform from which investigators might start forward without the necessity of being, as is so often the case, ignorant of what was already achieved, or of spending a great deal of time in a wild hunt through the almost boundless, but often scattered and inaccessible, ranges of Continental literature.

The plan of the present work has been to make the physiological action of remedies the principal point in discussion. A thoroughly scientific treatise would in each article simply show what the drug does when put into a healthy man, and afterwards point out to what diseases or morbid processes such action is able to afford relief. Unfortunately, in the great majority of cases our knowledge is not complete enough for this, and the clinical method has to be used to supplement the scientific plan.

I have added to the book a consideration of toxicology, so far as it is of interest to the physician. This has been done for several reasons. First, it was necessary to study the action of poisonous drugs upon man, in order to make out their physiological action; secondly, physicians are constantly required to diagnosticate and to treat cases of poisoning; thirdly, it is often of the greatest importance for a medical man in a court of law to be able to state what are the symptoms and post-mortem appearances produced by a given poison, what diseases they simulate, and how far and in what they differ from the phenomena of these diseases. That part of the science of toxicology which treats of the recognition of poisons in the cadaver, or in food and drink, belongs to the domain of the chemist, and I have avoided it altogether. For a similar reason, in the sections on materia medica, the chemical relations of mineral substances have not been discussed at all.

ABBREVIATIONS.

A. and N.—Alienist and Neurologist.
A. A. P.—Archiv für Anatomie und Physiologie.
A. de P.—Archives de Physiologie normale et pathologique.
A. E. P. P.—Archiv für experimentelle Pathologie und Pharmakologie.
A. G. M.—Archives générales de Médecine.
A. G. P.—Archiv für die gesammte Physiologie des Menschen und der Thiere.
A. Hk.—Archiv der Heilkunde.
A. I. B.—Archives italiennes de Biologie.
A. J. M. S.—American Journal of the Medical Sciences.
A. J. P.—American Journal of Physiology.
A. K. C.—Archiv für klinische Chirurgie.
Al. Z. Ps.—Allgemeine Zeitschrift für Psychiatrie.
A. M. Ex.—Archives de Médecine expérimentelle et d'Anatomie pathologique.
Am. Lan.—American Lancet.
An. d'H.—Annales d'Hygiène.
A. Op.—Archiv für Ophthalmologie.
A. Ph.—Archiv für Anatomie und Physiologie, physiologisches abteilung.
A. Pharm.—Archives de Pharmacodynamie.
A. P. I.—Archives de Pharmacodynamique internationales.
Aus. M. Gaz.—Australian Medical Gazette.
Aus. M. J.—Australian Medical Journal.
B. A. M.—Bulletin de l'Académie de Médecine de Paris.
B. A. R. B.—Bulletin de l'Académie Royale de Médecine de Belge.
B. G. T.—Bulletin général de Thérapeutique médicale et chirurgicale.
B. K. Ch.—Beiträge zur klinischen Chirurgie.
B. K. W.—Berliner klinische Wochenschrift.
B. M. J.—British Medical Journal.
B. M. S. C. P.—Bulletin et Mémoires de la Société Clinique de Paris.
B. M. S. J.—Boston Medical and Surgical Journal.
Cb. C.—Centralblatt für Chirurgie.
Cb. P.—Centralblatt für Physiologie.
C. B. S. A.—Correspondenzblatt der Schweizerische Aerzte.
Chi. M. J.—Chicago Medical Journal.
C. K. M.—Centralblatt für klinische Medicin.
Cl. M.—Clinica Moderna.
C. M. J. E.—Chicago Medical Journal and Examiner.
C. M. W.—Centralblatt für medicinischen Wissenschaften.
C. R. A. S.—Comptes-rendus de l'Académie de Science, Paris.
C. R. S. B.—Comptes-rendus de la Société de Biologie, Paris.
D. A. K. M.—Deutsches Archiv für klinische Medicin.
D. J. M. S.—Dublin Journal of the Medical Sciences.
D. Kl.—Deutsche Klinik.
D. M. W.—Deutsche medicinische Wochenschrift.
D. Z. Ch.—Deutsche Zeitschrift für Chirurgie.
Ed. M. J.—Edinburgh Medical Journal.
Fort. M.—Fortschritte der Medicin.
G. A. M. T.—Giornale della Reale Academia di Medicina di Torino.

G. H. M. C.—Gazette Hebdomadaire de Médecine et de Chirurgie.
Gl. M. J.—Glasgow Medical Journal.
Guy H. R.—Guy's Hospital Reports.
H. S. Jb.—Hoffmann and Schwalbe's Jahresberichte über die Fortschritte der Anatomie und Physiologie.
In. Dis.—Inaugural Dissertation.
J. A. M. A.—Journal of the American Medical Association.
J. A. P.—Journal of Anatomy and Physiology.
J. Chem. S.—Journal of the Chemical Society of London.
J. de l'A. P.—Journal de l'Anatomie et Physiologie.
J. de Th.—Journal de Thérapeutique.
J. Ex. M.—Journal of Experimental Medicine.
J. N. M. D.—Journal of Nervous and Mental Diseases.
J. P.—Journal of Physiology.
J. P. and B.—Journal of Pathology and Bacteriology.
Lyon M.—Lyon Médicale.
L. M. R.—London Medical Recorder.
M. C. Tr.—Medico-Chirurgical Transactions.
Med. R.—Medical Register.
M. M. W.— Münchener medicinische Wochenschrift.
M. News.—Medical News.
M. S. Rep.—Medical and Surgical Reporter.
M. T. G.—Medical Times and Gazette.
N. Cb.—Neurologisches Centralblatt.
N. Y. M. J.—New York Medical Journal.
N. Y. M. R.—New York Medical Record.
O. M. R.—Ohio Medical Recorder.
Pa. M. S. J.—Pacific Medical and Surgical Journal.
Path. Intern.—Pathologie Interne.
P. J. and Tr.—Pharmaceutical Journal and Transactions.
P. M. C. P.—Pester medizinisch Chirurgische Presse.
P. M. J.—Philadelphia Medical Journal.
P. M. T.—Philadelphia Medical Times.
P. P. S. L.—Proceedings of the Physiological Society of London.
Pract.—Practitioner.
Press. M. B.—La Presse Médicale Belgique.
Prog. M.—Le Progrès Médicale.
Q. J. P. M.—Quarterly Journal of Psychological Medicine and Medical Jurisprudence.
R. M. S. R.—Revue Médicale de la Suisse Romande.
Rif. M.—La Riforma Medica.
Sb. G. W.—Sitzungsberichte der königliche Gesellschaft der Wissenschaften.
S. Jb.—Schmidt's Jahrbücher der in- und ausländischen gesammten Medicin.
St. L. M. S. J.—St. Louis Medical and Surgical Journal.
S. L. P. C. Y.—Studies from the Laboratory of Physiological Chemistry of Yale University.
T. G.—Therapeutic Gazette.
Th. M.—Therapeutische Monatshefte.
Tr. R. S. Ed.—Transactions of the Royal Society of Edinburgh.
U. M. M.—University Medical Magazine.
U. N. M. T.—Untersuchungen zur Naturlehre des Menschen und der Thiere. Moleschott.
U. P. L. W.—Untersuchungen aus den physiologisches Laboratorium zu Würzburg.
V. A. P. A.—Virchow's Archiv für pathologische Anatomie und Physiologie.
W. A. W.—Sitzungsberichte der kaiserlichen Akademie der Wissenschaften zu Wien. Math. Naturwiss. Kl.
W. G. H.—Wochenschrift für die gesammte Heilkunde.
Wb. G. A. W.—Wochenblatt der k. k. Gesellschaft der Aerzte in Wien.
W. M. Bl.—Wiener medicinische Blätter.
Z. B.—Zeitschrift für Biologie.
Z. K. M.—Zeitschrift für klinische Medicin.
Z. Mb.—Zeitschrift für Medicinalbeamte.
Z. P. C.—Zeitschrift für physiologische Chemie.

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A TREATISE ON THERAPEUTICS:

COMPRISING

MATERIA MEDICA AND TOXICOLOGY.

INTRODUCTION.

In the treatment of acute disease it is essential that the doctor in charge superintend very carefully the nursing and hygiene of the sick-room, since the result of treatment may depend even more upon these so-called minor considerations than it does upon the administration of drugs. In the treatment of chronic disease the best results are to be achieved by the regulation of the habits and mode of life of the patient, and by the employment of certain remedial measures other than drugs. Of late years modes of treatment other than medication have become so important that they are here considered at length, requiring that the book should be divided into two parts. In the first of these are discussed those methods of therapeusis which are independent of medicinal substances, while the second part is devoted to the consideration of drugs.

THERAPEUTICS:

ITS PRINCIPLES AND PRACTICE.

PART I.

REMEDIES, REMEDIAL MEASURES, AND REMEDIAL METHODS WHICH ARE NOT DRUGS.

CHAPTER I.

GENERAL CONSIDERATIONS—MASSAGE—FEEDING OF THE SICK.

GENERAL CONSIDERATIONS.

In the treatment of chronic disease it is of the utmost importance that the physician inquire minutely into the personal habits of the patient and insist upon their regulation in accordance with the needs of the case. The importance of the alcoholic habit as a cause of local and constitutional disease is recognized by many who fail to perceive as clearly the effects of the excessive use of other stimulants. Insomnia, general nervousness, and various cardiac derangements are frequently the result of the tobacco-habit, and will not yield to any treatment until the abuse is corrected. Headache, general unrest, nervousness, and many other symptoms may be the outcome of excessive tea- or coffee-drinking, and especially is this the case when these nerve-stimulants are employed to enable the victim to continue excessive labor. Among the lower classes, and pre-eminently among sewing-women, the nervines just mentioned frequently replace substantial food, and the resulting headaches and nerve-failure are to be relieved only by a total alteration of the food-habits. The physician should also carefully study the clothing of his *clientèle:* especially is this necessary in regard to young children. Some mothers so overload the child as to keep the skin in a condition of habitual relaxa-

tion, impeding the natural, free movements, and causing general overheating. More frequently, however, young children are clothed too little than too much. Bare legs and bare arms in cold climates are fertile sources of illness. There cannot be two opinions in regard to the superiority of wool over cotton as a material for underclothing. The well-known effect of wet clothing in causing colds is due to the rapidity with which it conducts heat away from the body. Wet cotton is almost as good a conductor of heat as water itself, whereas woollen garments when wet still resist the passage of heat. During exercise cotton underwear becomes damp with perspiration, and in the subsequent cooling of the body fails almost entirely as a protective, whereas a woollen shirt under similar circumstances maintains the temperature of the vital organs. Modern merino underclothing is essentially cotton, and is entirely unfit for wear by delicate persons in cold or changeable climates. Persons who suffer from frequent catarrhs or are of a rheumatic or gouty diathesis, or whose nutrition is habitually feeble, should always wear next to the skin either wool or silk. When the question of expense is not vital, heavy silk undergarments are as serviceable as those made of wool, and, indeed, in rheumatic cases, in our experience, are superior to woollen underwear. In very many persons, and especially in those who suffer from frequent diarrhœas and indigestions, or derangements of the abdominal viscera, the abdominal bandage should be habitually worn, in addition to the ordinary underclothing. It should be sufficiently wide to cover the whole abdomen, should be either of silk or of wool, and should be so made as to be readily put on and to fit closely to the body. A simple piece of flannel of sufficient size, secured in its place by means of ordinary safety-pins, makes, perhaps, as serviceable an abdominal bandage as can be obtained. Both abdominal bandage and underclothing should be worn at night, although, for purposes of cleanliness, it is preferable to change them upon going to bed.

The physician should always inquire into the bathing-habits of the patient. Cleanliness and the maintenance of the proper condition of the skin require the use of the bath at least twice a week. In some very delicate persons the general bath produces marked depression, but this can almost always be avoided by the use of very hot water. If the hot or warm bath be employed habitually, it should be preferably taken at night, and, unless under very exceptional circumstances, the hot bath should always be immediately followed by cold sponging or the cold shower-bath, or by a plunge into cold water.

MASSAGE.

The term massage is used as the generic name for external manipulations which are employed for the purpose of affecting the nervous and muscular systems and the general circulation. From time immemorial such procedures have been used upon both man and domestic animals. In the sick-room, in the arena, upon the race-course, and in the luxurious

pursuit of health their usefulness has been abundantly proved by the ancient Greeks and Romans, by modern civilized nations, and by barbarous or semi-barbarous people. As remedial measures they were spoken of in the writings of the Chinese three thousand years before the Christian era, and were fully recognized by Hippocrates and Celsus.

Massage is not rubbing of the skin, although it has in all probability grown out of the practice of such rubbing. *General massage* is practised to affect the general condition of the body. *Local massage* is for the relief of local affections.

The methods of massage are so complicated that their discussion requires more space than can be here spared for them. Moreover, they can scarcely be learned even from the largest volume treating solely upon the subject, but must be acquired by practice under the guidance of a person having the necessary technical knowledge. A masseur must have sufficient knowledge of anatomy to understand the general drift of the circulation and the positions and shapes of the muscles and of the muscle-masses, must be cleanly and agreeable in person, and must be possessed of the proper technical skill. Especially is this true when the attempt is to treat local disease. Under such circumstances a really accurate knowledge of the shapes and positions of muscles, tendons, joint surfaces, and other portions of the affected limb is essential. Unless under very peculiar circumstances, the sex of the operator should be that of the patient.

Massage is usually practised upon the bared skin, and we think that this is preferable, although we have known skilful and successful manipulators who preferred that the patient should have thin, tight-fitting underclothes. The question as to whether the skin should be anointed before massage is one concerning which practice differs. The object of massage is to affect, not the skin, but the underlying tissue, and when there is special sensitiveness or irritability of the skin there can be little doubt as to the imperative necessity of some ointment. Vaseline may be employed. A very excellent material is pure and fresh cocoa-nut oil. Only so much of the grease should be used as is necessary to render the skin soft and pliable and to enable the fingers to glide easily over it.

Without entering into any detailed discussion of the physiological action of massage, it is sufficient to point out that general massage acts very much like general exercise, without the attendant expenditure of nerve and muscular force on the part of the patient.

During prolonged muscular inaction, whether from indolence, disease, feebleness, or other cause, the muscular structure itself suffers some degradation and the peripheral circulation becomes very feeble. Much of the albuminous liquid which escapes from the blood-vessels and diffuses itself through the tissues, after serving the purposes of nutrition, is taken up by the lymphatic system and returned to the great blood-vessels. If there be any *vis a tergo* driving this liquid from the periphery to the centre, it is so feeble that the return of the juices depends chiefly upon the squeezing of the various juice-channels during muscular contractions. During ha-

bitual inactivity the movement of fluids in the lymph-channels outside of the blood-vessels is excessively sluggish, and it is one great object of the stroking movements in massage to force these juices onward ; it is for this reason that these movements are directed from the periphery towards the centre. It is not probable that the whole effect of the stroking is mechanical. The influence of peripheral nervous irritations upon internal organs and upon the general circulation is recognized by almost every one, and every invalid knows the power of soothing strokes and touches in relieving nervousness and even pain. General stroking movements, if properly administered, are to most persons very quieting, and not rarely, when opportunity is afforded, general massage is followed by quiet sleep.

The kneading and percussion movements of massage act chiefly upon the local circulation, increasing its activity in the same way that spanking causes a blush upon the young. Kneading performs, however, still another function. Under certain circumstances the fibres of muscles within their sheaths or the neighboring individual muscles through their sheaths become agglutinated, and even the skin itself may get to be abnormally tense and attached to the subdermal tissue,—a condition which, when it occurs in the lower animals, is known as "hide-bound." Moreover, gouty or inflammatory exudations may form in almost any portion of the body. Kneading especially has power to mechanically loosen agglutinated fibres, to break up masses of exudation, and to so stimulate the local circulation in deeply seated tissues as to cause exudations to disappear or even glandular and lymphatic enlargements to be reduced.

General massage is employed advantageously in various neurasthenic conditions, and forms an important part of the system of treatment known as the Rest-Cure (see page 17). When there is marked feebleness or nervousness, massage should at first be practised very gently, but, except in rare cases, it will soon be found grateful to the patient. During the processes of the rest-cure, both massage and the faradic current will frequently reveal the existence of unsuspected spots of tenderness in various parts of the body. Such tenderness marks local congestion, or very often gouty exudation, and the best results follow from the gradual but persistent application, day after day, of increasingly powerful massage, often aided by very rapidly interrupted faradic currents, to the centres of tenderness, which almost invariably disappear sooner or later. Closely allied to these sore spots is the tenderness of the so-called spinal irritation, or spinal anæmia. When this spinal tenderness is pronounced, great care is necessary in the gradual application of massage and the faradic current to the affected region. If the operator be sufficiently careful at first to work only upon the borders of the tenderness, and gradually to approach the centre, excellent results can usually be obtained. Under these circumstances massage is useful not only as part of the general plan of treating the constitutional condition, but also by its local power in dispersing congestions and allaying nervous irritations.

The first séance in general massage should not last longer than half an

hour, but in a little time a full hour will be required. When there is lack of digestive power, constipation, or any similar symptom,—the outcome of sluggishness of the abdominal circulation and nerve-supply,—local massage of the abdominal and pelvic regions should be freely employed.

Abdominal massage for the purpose of affecting circulation in the intestines should be performed as follows. For one or two moments the abdominal muscles themselves should be kneaded, the individual movements being transversely directed across the muscle-fibres ; next, in order to influence the small intestines, a series of circular sweeping strokes should be made around the umbilicus, one hand following the other rapidly so as to complete the circles, firm pressure being instituted with the outer portion of the palms ; then kneading movement should be performed, beginning at the region of the ileo-cæcal valve, each movement being transverse to the course of the large intestine, the series of movements following the large intestine upward to the hypochondriac region, then transversely, and finally downward along the whole course of the colon. In some cases, especially when there is enlargement of the liver with torpor, good is to be achieved by kneading movements directly over and upon the diseased organ. When along with the enlargement of an abdominal viscus there is a condition of softness, great care should be exercised not to injure the organ by too firm pressure. This applies especially to the pulpy condition of the spleen sometimes seen in malarial disease.

Local massage is of great value in the treatment of *sprains*, chronic *inflammations of the joints*, and various other surgical affections, but should rarely be practised when the symptoms of the inflammation are at all acute. In subacute or chronic *rheumatism* affecting muscular or fibrous tissue it is of great value, especially when combined with judicious passive movements. Under its practice adhesions are broken up, exudations are dispersed and finally absorbed, and the natural condition of the parts restored.

In various forms of *paralysis* local massage is very useful in maintaining muscular nutrition. When the nerve-lesion is in the cerebrum, the muscles do not suffer in their nutrition, except secondarily from inactivity, and massage is usually not required in the early weeks of the affection. After a stroke of *hemiplegia* it is rarely proper to begin massage for two or three weeks ; but whenever the temperature of the arm decidedly and permanently falls, or serous exudation into the cellular tissue marks a loss of vascular tone, or when evidences of returning control over the muscles are manifest, local massage is often of service. At first the séance should not last more than five minutes, but after a time it may continue for ten or even fifteen minutes. In those forms of palsy, such as *infantile paralysis*, in which the trophic centres in the spinal cord are especially implicated, massage is of great importance. In acute cases it should be commenced as soon as the subsidence of fever and other symptoms of constitutional irritation marks the passage of the first stage of

activity in the spinal lesion. When the infantile paralysis develops gradually, massage may be employed as soon as the paralysis is recognized. It does not directly influence, to any extent, the fundamental spinal lesion, but, by maintaining a healthy condition of the peripheral apparatus, is of the greatest service in those cases in which there is a tendency to more or less complete repair of the structure of the spinal cord. In various *local paralyses*, as from pressure, from rheumatic affections of the nerves, or from other temporary or removable conditions of nervous or muscular tissue, massage may do much good. When the loss of power in a muscle is due to direct violence, as occurs with especial frequency in the deltoid muscle from falls on the shoulder, massage should be assiduously employed as soon as the primary inflammation produced by the injury has subsided. In such cases the treatment is of especial advantage in dispersing exudations and restoring the muscles and the muscle-fibre bundles to their normal relations and their normal looseness.

FEEDING OF THE SICK.

The present article is not a treatise upon diet or dietetics ; the books upon this subject are sufficiently numerous, but their scope is often too wide for the needs of the medical practitioner. In elaborate discussions upon the contained percentage of nitrogen and general food-qualities of various articles of diet, upon the cost and commercial history of foods, upon the amount of food necessary to sustain life, and upon the most economical forms of military, prison, and hospital rations, etc., the consideration of the feeding of the sick in private practice is often so overwhelmed as to be lost entirely. We propose to give here a brief practical summary of the methods of feeding in sickness when pecuniary considerations are of secondary importance.

The proper feeding in acute diseases accompanied by high fever varies to some extent according to the individual affection, but is subject to general principles which are sufficient practical guides for most cases. All such acute diseases are for present purposes readily divided into those in which the acute febrile stage is very short and those in which it is prolonged. When the acute febrile stage is very severe and temporary, it is usually associated with a complete anorexia, which the practitioner may obey with safety. In the first day or two of the onset of an acute pneumonia, violent scarlet fever, or similar affections, there is no cause for alarm even if the patient take no food. The digestive power at this time may be in complete abeyance. After, however, the first day or two of such an attack, and whenever the febrile reaction is prolonged, a loss of appetite amounting even to a disgust with food is no excuse for abstinence. All such states, with their accompanying diseases, tend to fatal result through exhaustion, and much can be done by proper feeding to prevent complete failure of vital power. The older writers upon dietetics taught that a fever patient was not to be fed, and some modern authors reiterate the old dictum. Fever is not, however, any contra-indication to food.

It is, indeed, usually associated with loss of digestive power, and if under such circumstances the stomach be overloaded with coarse food the symptoms will be aggravated by the resulting acute indigestion. The amount of nourishment received by a body is measured, not by the amount of food put into the stomach, but by the amount which is assimilated; and in febrile complaints the effort of the physician must be directed, not to the filling of the stomach, but to the obtaining of as large an assimilation of food as is possible without disturbing the alimentary canal. Any symptoms of gastric or intestinal disturbance should be the signal for the immediate lessening of the food. Such gross manifestations as vomiting, sour or nauseous eructations, and gastric distress are perceived at once by the most careless; but in typhoid fever we have seen skilful practitioners overlook the real cause of an excessive tympany or an increased diarrhœa, and continue the overfeeding while attempting to relieve these symptoms by medicine. Such practice is exceedingly reprehensible. In febrile adynamic diseases the feeding should be at short intervals, with small amounts of liquid food of a nutritious, easily digested character, and our own experience leads us more and more to the habitual use of foods which have been partially digested artificially.

The question of night-feeding in severe cases is an important one. Our belief is that death occurs much more frequently in adynamic diseases between one and five o'clock in the morning than at any other time,—a circumstance largely attributable to the habitual withholding of food and stimulants during the night. Sleep is essential to the recuperation of vital force, but an exhausted patient usually goes to sleep readily after the partial awakening which is sufficient for the administration of a milk punch, or else sleeps in so broken a manner that the careful nurse can give the food at short intervals without awakening him. In no typhoid case of severe type should an interval of more than three hours be allowed to elapse at night without food and stimulants, and the amount given at a single time should be so increased that almost as much will be taken during the night as during the day.

In typhoid cases alcohol in some form should be given with the food, in not too large proportion. Alcoholic liquors in moderate amount stimulate the stomach and aid digestion and absorption, but in large amount interfere with these processes. It may be set down as a general rule with few exceptions that all foods given in protracted febrile states should be in liquid form.

Liquid foods may be divided into Liquid Meat Foods, Milk Foods, and Artificially Digested Foods.

Liquid Meat Foods.—It must be remembered that all articles of the present class are stimulants rather than nutrients. Most of them do not contain more than one per cent. of albuminous substances. Under this heading we include all liquid preparations of meat made without artificial digestion.

At one time these liquid preparations of meat were supposed to repre-

sent the whole nutritive value of the meat, but recently all nutritive power has been denied to them. They contain kreatin, kreatinin, sarkosin, sarkin, xanthin, kreanin, inosite, fat, and inorganic salts, with a very small amount of albuminous principles. It is not probable that any of these substances, except the albumin and the fat, are capable of being assimilated and used as food. The experiments of Kemmerich also indicate very strongly that they are not nutrients, for he found that animals fed exclusively upon these preparations died even more quickly than those left to starve. There can be no doubt that death under these circumstances was largely due to the depressing effect of the inorganic salts contained in the extracts. Clinical experience, in a measure, conforms with this scientific reasoning. At a time when beef essence and beef tea were very largely relied upon as nutrients in Philadelphia, it was found that they acted better when milk was also given. In his earlier trips into the wilderness, involving much physical labor, H. C. Wood took with him the best artificial meat extracts to serve as condensed food, but, after a few trials, found that they were unable to sustain prolonged effort,—as the guides put it, "they do not stick to a man's ribs,"—and, although at that time the theory was that they were concentrated nourishment, practical experience soon led to their abandonment. Although of little use as food, these substances are valuable stimulants, and may by reviving temporarily an exhausted patient prepare the way for the digestion of food. In a series of experiments made upon the frog's heart by Thomas J. Mays (*Therap. Gaz.*, vol. ii. p. 152), it was found that the artificial beef extracts and concentrated beef preparations had a very decided influence in maintaining the activity of the systoles. Notwithstanding Mays's arguments to the contrary, however, we believe that the effect of beef extracts upon the frog's heart is entirely similar to that of the phosphate of calcium (see CALCII PHOSPHAS). In typhoid and other similar low fevers it is an excellent plan to give beef essence or beef tea alternate hours with milk punch. During convalescence a hot bowl of beef tea or beef essence after exertion such as carriage-riding, walking, etc., may act very well as a stimulant. By the addition of various substances these liquid preparations of meat can be made nutritive : thus, an egg rapidly stirred into a bowl of beef essence forms a very useful stimulating food. There are in the market various extracts of beef claiming to represent, in a solid form, beef essence. The better forms of these articles undoubtedly do represent in great part beef essence, but they are distinctly inferior to the freshly made preparation in taste, and in containing no albumin : so that it is always better to employ the fresh beef essence if it can be procured.

Liquid meat foods are divisible into those that are raw and those that are cooked. Of the raw foods of the class, the best is *meat juice*. This is made, according to the directions of Pettenkofer and Voit, by selecting lean meat from the round of beef, cutting it into small pieces, and expressing the juice in a press of sufficient power,—such as now can be pur-

chased at any of the larger drug-stores. This juice contains, in addition to the salts and extractives, the albumin that remains fluid after the rigor mortis,—chiefly serum-albumin and coloring matters. The proportion of albumin is about six per cent.: by heating the albumin is precipitated, but it is not affected by salt or by mere warming.

Meat juice is a valuable preparation when a powerful stimulation is desired and the digestive forces are exceedingly weak, as in the feebleness or collapse that follows cholera infantum and other infantile diarrhœas. Its taste is that of raw meat, and is so disagreeable to many persons as to prevent its use.

Liebig's beef tea is made by adding seven ounces of water and three or four drops of hydrochloric acid to one and a half pounds of lean beef, allowing to stand one hour, passing through a hair sieve, and washing out the meat with three ounces of water. This infusion contains, on the average, not more than one per cent. of albumin. The hydrochloric acid added to the water is not sufficient to dissolve the myosin of the muscle : so that this preparation can be looked upon as nothing more than a dilution of meat juice, and is very inferior. To have any effect it must be given in enormous quantities.

The cooked concentrated liquid forms of meat extracts are beef tea and beef essence. Neither of these can be considered to have distinct nutritive value. It is very rare for them to contain more than one per cent. of albuminous substances; but they are powerful stimulants, and for such purposes are as useful as the expressed meat juice.

To make *beef tea*, cut one pound of round of beef into small cubes not larger than half an inch in diameter; soak for two hours on the back of the range, in an earthenware pipkin, with one pint of cold water, and allow to simmer for about fifteen minutes, and finally to boil for three minutes; add half a teaspoonful of salt and pepper, *pro re nata*.

To make *beef essence*, prepare the meat as for beef tea ; put it into an earthenware bottle without water and loosely cork ; set this in a pot of cold water and bring very gradually to the boiling point ; boil for twenty minutes or half an hour.

Soups are liquid preparations which resemble beef tea and beef essence in containing the extractives of meat, but which differ from these preparations in having in them various nutritive substances. Soup is therefore both a stimulant and a nutrient, the amount of nutrient material varying greatly according to the preparation of the soup. The lighter forms of soups are commonly spoken of as broths. They may be used when the stomach rejects less readily digested forms of food.

To make *chicken broth*, take three pounds of chicken well cleaned, cover with cold water, boil from three to five hours (until the meat falls to pieces), strain, cool, and skim off the fat. To a pint of this add salt and pepper and two tablespoonfuls of soft rice which has been previously thoroughly boiled in salt water ; bring the broth to a boil. In preparing the rice, half a cupful should be boiled for thirty minutes with a teaspoonful of salt in a pint of water. To make *mutton broth*, take one pound of lean, juicy mutton, chopped fine, and proceed as with chicken broth.

In the preparation of soups the first thing is the making of the so-called stock, or basis for the soup. There are two distinct stocks: one which may be known as the brown stock, the other as clear stock or *consommé*.

To make *brown stock*, take four pounds of shin of beef, four quarts of cold water, ten whole cloves, four peppercorns, a bouquet of herbs (sweet marjoram, summer savory, thyme, and sage), one tablespoonful of salt, three small onions, one turnip, one carrot, two stalks of celery, two sprigs of parsley. Cut the meat from the bones, after which place the bones and one-half of the meat in a soup-kettle and allow to stand for half an hour in the cold water. Heat gradually, and allow to simmer for six or seven hours. Brown the remainder of the meat in two tablespoonfuls of beef-drippings, and add with the other meat and with the vegetables chopped fine, when the kettle is put on the fire to simmer. After it has simmered the required time, strain the stock and set aside to cool, the fat being removed from the top. The stock is then ready for use.

To make *consommé* or *clear stock*, proceed in exactly the same way as for brown stock, except that three pounds of the knuckle of veal are to be added to the meat, and all the meat is to be put in at once without browning. After the stock has been formed, in order to clear it add the white and the shell of one egg and the juice and rind of one lemon, beating them all up together; then put on the fire, bring to the boiling point, strain through a sieve, and again through a napkin, without pressure or squeezing, and serve.

In making the soups the stocks must never be allowed to boil, or at most must be brought only for a moment to the boiling point.

To make *Julienne soup*, put one pint of the brown stock on the fire to heat, after which a pint of finely chopped vegetables (turnip, carrot, etc.), with half a teaspoonful of salt, should be put on with a little water to parboil. This being done, add the vegetables to the stock, and season with half a saltspoonful of pepper. *Vermicelli soup* is made by adding half a cup of vermicelli to a pint of the brown stock. Cook the vermicelli for ten minutes in salted boiling water, season with a half-teaspoonful of salt and a half-saltspoonful of pepper, and add to the warm stock.

A very elegant stimulating and nutritious soup can be made out of *consommé* by boiling ordinary pearl sago in salt water for from two to three hours, until the grains become swollen almost to bursting, and then stirring the sago into the *consommé* while still boiling.

Milk Foods.—Of all liquid foods milk is the best and the most generally applicable to the treatment of disease. Cow's milk contains, in round numbers, 87.5 parts of water, 3 parts of casein, 0.75 part of albumin, 3.6 parts of fat, 5 parts of sugar, and 0.07 part of inorganic salts. One pint of milk contains, in round numbers, 0.6 ounce of solid albuminous substance, 0.6 ounce of fat, and 0.8 ounce of sugar. When two quarts of milk are taken in the course of twenty-four hours, about two and a half ounces of fat are ingested,—an amount too great for an inefficient alimentary canal to digest, so that it is often necessary to skim the milk. As milk contains practically no indigestible residue, it leaves behind it in the alimentary canal no fecal matter, and its use therefore frequently pro-

duces constipation. In cases of diarrhœa this tendency to a binding action can be increased by boiling the milk, a process which coagulates the albumin of the milk and slightly lessens, if the scum be removed, its nutritive value. When milk is used very freely and the digestion is feeble, there is always danger of the formation in the stomach of a coagulum so dense that the gastric juice will not be able freely to penetrate it. This difficulty can usually be overcome by a little care. The addition of from half an ounce to an ounce of lime-water to every five or six ounces of milk has a distinct tendency to prevent too rapid and firm coagulation. Sipping milk instead of drinking it—in other words, putting the milk in the stomach in small quantities at a time—has a still greater power in repressing the formation of hard coagulum. When the digestive powers are feeble, milk should be taken slowly in small quantities at a time. In some cases it is very important that it be drunk hot, but without previous boiling.

There are various useful nutrient and stimulant foods prepared with alcohol in milk, as follows :

To make *wine whey*, bring half a pint of milk to the boiling point ; add half a pint of sherry wine, and allow to stand in a warm place for five minutes ; strain, and sweeten to taste. The whey which is left consists almost exclusively of wine and water, with milk sugar and milk salts. It contains very little nutriment, but is sometimes tolerated by the stomach which refuses other food.

To make *milk punch*, take half a pint of milk ; pour into it from a dessertspoonful to a tablespoonful of brandy, rum, or whiskey, according to the needs of the patient ; sweeten and spice with nutmeg to taste. This preparation represents all the nutritive value of milk and the stimulating effects of the liquor. If the stomach be at all delicate, a tablespoonful of lime-water should always be added to it before putting in the brandy.

To make *eggnog*. Eggnog is a heavy, rich, highly nutritive liquid, which must be employed in limited quantities, and very carefully when there is any delicacy of stomach. The yolk of one egg may be added to half a pint of milk, afterwards from half an ounce to an ounce of brandy, and the white then beaten in.

Sometimes when the stomach rejects almost all forms of food, the addition of carbonic acid water to the milk meets with success. Equal quantities should be employed, and the casein of milk should be coagulated in fine flakes. A light, powerfully stimulant beverage, somewhat similar to the one just mentioned, but to some palates more elegant, is made by the addition of champagne to milk.

There are certain forms of fermented milk which are valuable as being easily digested by the stomach and very acceptable to the palate. They also render possible some variety of food to persons largely restricted to milk diet.

Koumiss, or *kumys*, is a fermented liquid prepared by the Tartars from mares' milk. In this country it is made from cows' milk : it is to most persons a very agreeable beverage, which in nutritive qualities represents the same quantity of milk, and is by most stomachs much more easily digested. It is very well suited for the treatment of convalescence and of chronic diseases, though it may be used, often with great advantage, in acute febrile illnesses. Take an ordinary beer-bottle

with a patent shifting cork, put in it one tablespoonful of white sugar, one pint of milk, one-sixth of a cake of Fleischmann's yeast or one drachm of strong liquid yeast, shake well, allow to stand from eight to ten hours in a temperature of from 85° to 95° F., shake well, and put upon the ice to cool. This ought to be used within twenty-four hours after being made. The longer the fermentation is allowed to continue the more sour is the koumiss ; and its condition should be regulated to suit the individual palate and stomach of the patient. If it be desired, it may be flavored by the addition of a small piece of vanilla bean to the milk before fermentation.

Matzoon differs from koumiss in that it contains no carbonic acid, is thicker, and more cheesy in its flavor. It occurs in the market in various brands, but we know of no practical method of making it at home. It is the product of a peculiar fungus known as the kefir ferment.

Milk may be used as the basis of a number of farinaceous or starchy liquids. It must be remembered that these starchy compounds are more or less difficult of digestion, and during the progress of an acute, severe febrile illness they must be employed with the greatest caution. In convalescence and in chronic invalidism, however, they are often very serviceable. In making these preparations it is essential that they be closely watched and stirred, to prevent burning, unless they be cooked over hot water.

To make *oatmeal porridge*, stir two ounces (half a cupful) of crushed oatmeal into a pint of milk, previously warmed, and afterwards cook from twenty to thirty minutes ; add salt to the taste.

To make *baked flour porridge*, a very excellent porridge, of easy digestion, and especially valuable when there is a tendency to looseness of the bowels, take one pint of flour, pack tightly in a small muslin bag, throw it into boiling water and boil for five or six hours, cut off the outer sodden portion, grate the hard core fine, and stir into boiling milk to the desired thickness.

To make *arrow-root porridge*, stir two teaspoonfuls of arrow-root in half a teacupful of cold milk until a *perfectly smooth* mixture is made ; have on the fire a pint of milk, and, while this is boiling, add the arrow-root little by little, stirring constantly until cooked,—*i.e.*, from one to two minutes after the last is poured in ; add sugar, nutmeg, and wine, according to taste or the exigencies of the case. When milk is not to be had, or a very low diet is required, water may be substituted.

The secret of properly preparing arrow-root is in having the first mixture with milk absolutely smooth and free from lumps.

To make *chocolate porridge*, a very palatable gruel to many persons, mix together one-quarter pound of best chocolate, grated, one-half pound of rice flour, two ounces of arrow-root, and one-quarter pound of loaf-sugar, grated ; add a tablespoonful of this mixture to a pint of hot milk, and let it boil five minutes ; then remove the preparation from the stove and serve hot. It should have the consistency of gruel.

To make *tomato porridge*, a very excellent porridge or *purée*, highly nutritious and useful during convalescence, take one quart of canned tomatoes, bring to a boil, strain while hot through a hair sieve ; bring a quart of milk to a boil, add sufficient flour to make a thick paste, stir in, and continue to boil until the flour is cooked (about twenty minutes) ; stir the strained tomatoes gradually, a little at a time, into the boiling milk ; cook five or ten minutes, seasoning to taste.

To make *sago porridge* or *sago jelly*, wash the sago well in cold water, put a small teacupful of it in half a pint of water to soak overnight, and in the morning put this mixture into one pint of hot water ; squeeze into it the juice of a thinly

pared lemon, and allow to simmer slowly for twenty minutes ; then sweeten, add wine according to taste or the exigencies of the case, and pour into moulds to cool.

To make *tapioca porridge*, soak two tablespoonfuls of clean tapioca in two teacupfuls of cold water overnight ; in the morning add a little salt and one pint of milk, or water if milk is not allowed ; simmer until quite soft ; stir well while cooling ; when done, pour into a bowl, and add sugar, wine, and nutmeg, according to taste or the exigencies of the case.

Artificially Digested Foods.—In low fevers the powers of the alimentary canal are certainly much impaired, and foods which have undergone more or less complete artificial digestion outside of the body are very useful.

In all cases in which the typhoid symptoms are severe, milk should constitute the chief reliance, and should be partially digested before administration. When the disease is prolonged, and especially when the mental condition is clear, the patient frequently tires of milk. Under these circumstances various liquid foods prepared by the partial digestion of solids are of great importance. Artificially digested foods are also of value during convalescence, and their employment constitutes a very important part of the treatment of gastric and intestinal catarrhs. Most peptones have a distinctly bitter taste, which may be very objectionable in individual cases. This taste can be partially overcome by the addition of flavoring substances or extracts, and often may be altogether avoided by arresting the process of artificial digestion before completion.

At first thought pepsin would appear to be the most available ferment for the preparation of peptones ; but practical experience has led to reliance upon pancreatin. Pancreatin, pancreatic extracts, and pancreatic liquors are now found abundantly in commerce. The superiority of the secretion of the pancreatic gland as a practical ferment is connected with the fact that it contains two distinct classes of digestive principles,—namely, pancreatic diastase, which dissolves starch, and trypsin, which acts upon albuminous principles. It is of great importance to be able to determine readily the value of any preparation of pancreatin. The test devised by William Roberts (*Digestive Ferments*, London, 1881) appears to be very practical. If pancreatin be added to fresh milk without an alkali, in the course of a few minutes the liquid acquires the property of curdling abundantly upon boiling ; and Roberts estimates the value of a pancreatin by the number of cubic centimetres of milk which are transformed by one cubic centimetre of the sample at a temperature of 40° C. to the curdling point in five minutes. The liquor pancreaticus used by Roberts had a power oscillating between fifty and seventy. A test which may be substituted for that of Roberts, and which is especially applicable to the ordinary pancreatic extracts or so-called pancreatin, is based upon the peptonizing power of the powder. Five grains of it added to twenty grains of sodium bicarbonate should so alter the casein contained in one pint of milk at a temperature of 115° F. in an hour, that no coagulation will occur upon the addition of nitric acid.

To make *peptonized milk*, dilute a pint of milk with a quarter of a pint of water, heat to about 140° F., add two teaspoonfuls of liquor pancreaticus (Roberts's) with twenty grains of sodium bicarbonate, digest in a warm place for an hour or an hour and a half, raising momentarily to the boiling point; at the temperature of the sick-room, 65° F., the digestion will usually require about three hours. Or milk may be peptonized by dissolving five grains of pancreatin with twenty grains of sodium bicarbonate in an ounce of warm water, adding to a pint of milk, and keeping at a temperature of 110° F. for one hour. Thoroughly peptonized milk has a disagreeable bitter taste, so that in practice the peptonizing process is usually not allowed to come to completion. It must, however, be remembered that the taste is a test of the peptonizing, and that the so-called peptonized milk which has no bitter taste is simply milk mixed with pancreatin, nothing more. Probably the greater part of the peptonized milk given to the sick is practically simple milk.

To make *peptonized milk gruel*, prepare a thick gruel with arrow-root, oatmeal, sago, or other similar farinaceous articles, add, while still hot, an equal quantity of milk, and subsequently, when cooled to 100° F., for each pint twenty grains of sodium bicarbonate and two teaspoonfuls of liquor pancreaticus or five grains of pancreatic extract, digest in a warm place for two hours, boil the mixture momentarily, and strain.

To make *peptonized beef tea*, simmer half a pound of minced beef for two hours in a pint of water containing twenty grains of sodium bicarbonate, allow to cool to about 100° F., digest at this temperature with a tablespoonful of liquor pancreaticus or ten grains of pancreatic extract for three hours, decant and momentarily boil. This beef tea is said to be about equivalent to milk in nutritive value, containing 4.5 per cent. of organic solids, three-fourths of which is peptone.

To make *peptonized oysters*, a palatable and nutritious dish, mince six large or twelve small oysters, and add to them, in their own liquor, five grains of pancreatic extract with twenty grains of sodium bicarbonate; bring the mixture to 100° F., and maintain, with occasional stirring, at that temperature for thirty minutes, then add one pint of milk and keep the temperature steadily up for ten or twenty minutes; finally the mass is to be brought to the boiling point, strained, and served. Gelatin may be added, and the mixture served cold as a jelly. Cooked tomato, onion, celery, or other flavoring suited to the individual taste and condition of the patient may be added at the beginning of the artificial digestion.

To make *pancreatized milk toast*, digest soft milk toast for from thirty to fifty minutes with pancreatin and sodium bicarbonate until it becomes an almost homogeneous pulpy mass, which, when the crusts have been removed, is usually readily retained by the irritable stomach. In extreme cases, however, it may advantageously be strained and the fluid portion alone used, in which the partially peptonized solution of casein of the milk is reinforced by the actually digested gluten and starch of the bread, together with a very little dextrin. Plain, light sponge-cake may be similarly digested, and occasionally forms a desirable change.

Rectal Alimentation.—In severe gastritis and in gastric ulcer it is sometimes necessary to enforce a temporary or even a somewhat prolonged abstinence from food. In diphtheritic paralysis of the throat, as well as in strictures of the œsophagus, it may be almost impossible to get food into the stomach, and in various cases the food is vomited whenever it is ingested. Under any of these circumstances feeding by the rectum becomes a matter of the utmost importance. There is no reason for believing that the rectal or even the colonic secretions have digestive power. Absorption goes on slowly from the rectum, but, according to Landois, very rapidly from the colon itself. For these reasons injections which are

used for the purpose of nourishing the patient should be bland, concentrated, and thoroughly digested; peptonization should always be complete. Moreover, the material should be thrown high up into the colon. It should be given not oftener than three times in twenty-four hours, and the colon should be thoroughly washed out by a high injection of simple water at least twice in the twenty-four hours. If there be irritability of the colon, it may be necessary to add opium to the nutritive material injected. Again, in many cases whiskey or brandy may be very useful. In most cases it is best to give the injection not oftener than twice in the twenty-four hours, and to wash out the colon an hour before administration. The presence of a putrid odor in the discharges is evidence that more food is given than the colon can work up, and the colon is as much irritated by overfeeding as is the stomach. In colonic as well as in gastric feeding it is the amount absorbed and not the amount ingested that does good.

In 1872, from the pancreas of swine or cattle, W. O. Leube made a food preparation which he experimentally proved to yield nutritive material to the blood of dogs when injected into the colon, and by whose colonic exhibition he maintained life for four weeks in a patient whose stomach rejected all food. Leube's formula may be found in detail in the tenth edition of this book, but is here omitted because it has no superiority over preparations made with commercial pancreatic extracts. As milk and eggs contain all the food necessary for the sustenance of life, and are more rapidly and readily digested than is meat, all that is necessary is to digest them thoroughly before injection. From half a pint to a pint of milk with two or three eggs may be employed at each injection. If alcohol is to be given in any form, it should be added to the injection just before administration.

CHAPTER II.

THE TREATMENT OF SYSTEMIC STATES.

EXHAUSTION AND NEURASTHENIC CONDITIONS.

DEPRESSION is a condition of temporarily lowered vital activity produced by the presence of some poison in the system. Exhaustion is a condition of absolute lack of power in which the functional activity is repressed, not by a depressing substance, but by the inability of the affected part. In practice it is essential to distinguish between these two states. The one requires treatment by stimulants, while the other is often, although temporarily relieved, permanently aggravated by the use of stimulants. Exhaustion, especially of the nervous system, is frequently spoken of as a disease, under the name of *neurasthenia*. It is not a disease, however, but a condition, which may be the result of overstrain or overwork or of some chronic disease. It is essential that in every case of alleged neurasthenia very careful examination should be made to detect the presence of organic kidney disease, chronic diarrhœa, or other possible cause of the exhaustion. The amount of work necessary to produce neurasthenic exhaustion is dependent upon the original amount of power in the organism. In persons born of neurotic feeble parentage or of parents exhausted by overstrain, the working power may be very slight. Exhaustion may be local or it may be general. This applies to the nervous system as well as to the other apparatus of the body. A local nervous exhaustion tends towards developing into a general condition. Thus, a writer's palsy may be the first symptom of a general break-down. Spermatorrhœa, at first due purely to local exhaustion of the implicated nerve-centres, if unchecked very generally develops into general neurasthenia. The same is true of cerebral exhaustion following excessive mental work. The exhaustion is to be relieved only by recuperation, and recuperation is to be obtained only by rest and the assimilation of food. The nature of the rest depends upon the character of the exhaustion. In cases of pure cerebral exhaustion with the bodily powers untouched and the physical powers not much implicated, freedom from care and from all mental work, conjoined with life in the open air, is the essential of cure. It must be remembered that sight-seeing is as exhausting to the brain as is the hardest study, and that in extreme cases even the seeing of friends may overtax the brain, so that isolation may be essential. Such isolation may be obtained, if the bodily powers remain good, by travel in the wil-

derness, or on the ocean, or in other positions where intercourse with the world is impossible. In cases of extreme neurasthenia or nervous exhaustion the so-called rest-cure is a method of treatment of great value. It is essential for its successful employment that it be modified to suit the needs of the individual case : if employed as a set mould into which every case is to be forced, it will frequently do harm.

The principles of the rest-cure are absolute rest, forced feeding, and passive exercise. Absolute rest is often prescribed by the physician without being sufficiently definite and insisted upon. When it is desired to apply it most strictly, it should be clearly explained that the patient is not to be allowed to get out of bed even to pass urine or fæces, nor to feed himself or herself, nor perform any act of the toilet whatsoever. The rest also must be for the mind as well as for the body, and it is essential that the patient be isolated. In obstinate, severe cases of neurasthenia complete and absolute isolation is a *sine quâ non*, and especially when there is a decidedly hysterical element is it necessary to separate the patient entirely from her friends. Under these circumstances there must be a well-trained nurse who is personally agreeable to the patient. The confinement would be very irksome to any except the most exhausted patient were it not for the daily visit of those engaged in the treatment. To provide further against *ennui*, the nurse should be a good reader, so that under the definite instructions of the physician she can occupy a certain portion of the time in reading to the patient.

In order to maintain the functions of the skin, the patient should be well sponged with hot water in bed every morning after breakfast. A strong solution of salt, or, better, sea-brine, is to be preferred to simple water, and frequently it may be followed by the use of alcohol. In very feeble cases the alcohol may be employed alone. We have seen very good effects from momentarily rubbing each portion of the skin with ice just after bathing. When rubbing with ice is practised, the water used in the bathing should be as hot as can be borne. In giving the bath the patient should be stripped, and lie between blankets, so that exposure of the whole body is avoided while each part is thoroughly washed. No exertion on the part of the patient should be allowed. Women should not be permitted to arrange their own hair.

The question of feeding is one of great importance, and requires the utmost care and attention from the physician. The end to be attained is to feed the patient as much as can be digested, but not to overfeed and derange the digestion. Food should be given at intervals of two or three hours, and must be both light and nutritious. It should, at least at first, consist largely of milk, except in those rare cases in which that fluid does really disagree with the stomach and is not merely thought to do so. The milk should be skimmed or given in the form of koumiss. Beef juice and other concentrated meat essences are valuable as stimulants, and may be used especially as the basis of soups. Various farinaceous articles of food may be added to them : if an egg be stirred into the concentrated bouillon

or beef essence just as it ceases boiling, a nutritious and to many persons palatable dish is obtained. When constipation exists, oatmeal porridge, Graham bread, and fresh or dried fruits may be allowed if readily digested by the patient. In order to give an idea of a general plan of the dietary, the following schedule of the daily life is given. It must be altered from day to day, so as not to weary the patient by its monotony. Such a schedule should always be put in the hands of the nurse, who should be required to follow it strictly. Success will in a great measure depend upon the practical skill and tact of the physician in his adaptation of the diet to the individual requirements of the case :

8 A.M. Rolls or toast; cocoa or weak coffee, or roasted wheat coffee; beefsteak, tenderloin, or mutton-chop.
9 A.M. Bathing.
11 A.M. Oatmeal porridge, with milk, or else a pint of koumiss.
12 M. Massage.
2 P.M. Dinner: bouillon with or without egg; beefsteak, rice, roast white potatoes; dessert of bread-pudding, blanc-mange, or similar farinaceous articles of diet.
4 P.M. Electricity.
5 P.M. Milk toast.
9 P.M. Half a pint of skimmed milk or koumiss.

In many cases the patient at first can take very little food, and it is frequently best to begin the treatment with an entirely liquid diet, giving milk every two hours, or some nutritious soup, with milk or plain farinaceous food, and only after a time gradually accustoming the patient to solid food. Not rarely a prolonged treatment by the so-called milk diet is of avail. The rest-cure is, indeed, largely based upon a careful regulation of the food.

Passive exercise is to be obtained by the use of electricity and massage, the object being to get the effects of exercise upon the nutrition and circulation without the expenditure of the patient's nerve-force. By the use of electricity muscular contractions are secured that simulate those which are voluntary, and more or less thoroughly replace them.

The faradic current is alone used. It is applied in two ways : first, to the individual muscles ; second, to the whole body. The séances should be daily, the operator beginning at the hand or the foot, and systematically faradizing each muscle of the extremities and the trunk.

The slowly interrupted current is generally preferable, but advantage is sometimes gained by varying the rapidity of the interruptions. The general rule is to select that current which produces most muscular contraction with the least pain. The poles should be applied successively to the motor points of the muscles, so as to contract each firmly and thoroughly. This process should occupy from thirty to forty minutes. The electrodes are then to be replaced by large sponges well dampened with salt water : one of these should be put at the nape of the neck and the others against the soles of the feet, and a rapidly interrupted current

as strong as the patient can bear, should be sent through the body for twenty minutes or half an hour. It is unnecessary for the physician to remain during this time. In some cases the electrical programme may be varied so as to get a local stimulant action from the general current. Thus, when digestion is enfeebled and the bowels are costive, for a portion of the time one of the sponges may be placed upon the epigastric region. In women, when there is great abdominal and pelvic relaxation, one pole may be placed high up in the vagina. We have seen old-standing prolapsus cured in this way.

The principle of rest-cure for the relief of exhaustion has a very wide application. Thus, in the treatment of acute diseases, such as typhoid fever, in which death results from exhaustion, it is of the utmost importance that absolute rest be prescribed very early. Before the diagnosis can be certainly established, and when there is merely a suspicion of typhoid fever developing, the patient should be put to bed, and should not be allowed to get out for any purpose. One great object of nursing is the saving of the strength of the patient and the prevention of exhaustion by disturbance. Mere uncleanliness, a low voice to a deaf patient, a loud, high-pitched voice to one whose hearing is acute, failure to understand quickly the whims and caprices of a sick man or woman, are tormenting things, which may take away the rest and even destroy the life of a patient. It is almost equally essential that all fussiness be avoided. The nurse who is continually asking the patient whether he will have this or that, or wants this or that, or is shifting the blinds, or fixing the furniture, or moving about unnecessarily, may not only be disagreeable, but may do great harm.

In applying the rest-cure to the treatment of the individual case, it must be remembered that the system is based upon certain principles, and that these principles are frequently, in the individual case, best carried out by a modification of the details of the plan which has been given. Not rarely advantage is obtained by daily sending the patient out carriage-riding, or even from taking walking exercise once a day. In other cases the rest-cure may be very advantageously combined with more protracted out-door life and exercise, the patient being required simply to pass twelve, fourteen, or sixteen hours out of the twenty-four in bed and the remaining time in the open air. It is impossible, within moderate scope, to describe all the modifications of the method which will occur to the skilful physician.

The time of continuance of the rest-cure varies greatly: even in extreme cases the patient should be allowed to sit up at the end of six or at most eight weeks, and in many instances three weeks of seclusion is all that is absolutely essential. The period of convalescence requires care. An attempt to return rapidly to the performance of household duties or to the ordinary labors of life will usually dissipate the acquired strength, and for the gain to be permanent it is in most cases necessary that the patient be sent to some quiet sea-shore, mountain, or country resort, in

order by out-door life and gradually increasing exercise to harden into permanent form the flesh and strength which have been laboriously gathered.

TREATMENT OF CORPULENCE.

In the treatment of corpulence it must be remembered in the first place that the same line of treatment is not suitable for every case. Speaking broadly, we may divide cases of corpulence into two classes (excepting those associated with some apparent organic cause) : those due to defective oxidation and those due to excessive food-supply. The patients of the first class are mostly anæmic and of little muscular power, while those of the second are plethoric and robust, and their excretion of urea is, as a rule, much above normal.

For the purposes of prognosis this division of obesity is very important. In the overfed, reducing the food-supply may be all that is needed ; in the so-called "fat anæmics" it may be very difficult or perchance impossible to increase oxidation ; hence in those who are at once fat and feeble the prognosis is grave in proportion to the feebleness. For the purposes of therapeusis the division is not so important as it may seem at first sight, excepting in so far that it points out that in a fat anæmic the effect of regulating the diet is less than it is in those who are obese and plethoric. In each class it is essential to increase oxidation as much as possible, since few persons will tolerate prolonged semi-starvation. The fat anæmic often, however, bear rigid dieting badly, and with them, therefore, great care must be exercised in the reduction of the food.

Certain drugs have some influence in increasing oxidation ; in the anæmic, iron seems to increase the activity of the destructive processes of the body and to aid in reducing flesh. On the other hand, in such subjects the alkalies, especially the potash salts, though they increase tissue-waste, may be harmful and augment the weakness. Contrariwise, however, when there is an abundance of strength in an obese subject, the continuous use of alkalies, and especially of alkaline laxatives, may be of great service. It must be remembered that very often in these cases there is lack of activity in the intestinal glands and much retention of half-assimilated materials.

The value of Kissingen, Carlsbad, and other alkaline purgative waters, and the results sometimes obtained in obesity by treatment at the various alkaline spas, are very familiar ; but the alkaline laxative ought to be, as it is in fact at the various springs, used only as an adjuvant to the more serious treatment. The keeping of the patient in a state of chronic purgation is, after all, but a crude method of affecting metabolism, and if too prolonged may have a local injurious effect on the intestinal tract.

The use of the thyroid gland in obesity will be considered at greater length in another portion of this book. It is enough here to point out that the extract of the gland does increase oxidation of the carbohydrates of the body, and that therefore it is often useful in the treatment of

obesity as an addition to the regulation of the food and the use of exercise. Given in excess it produces deleterious results, and when used for too long a time appears to largely lose its power.

The natural and most important means at command for the increasing of oxidation is exercise, and the practice of regulated exercise is at the basis of all proper systems of weight-reduction.

The amount and form of exercise to be prescribed in any individual case depend upon the peculiarities of the patient and his surroundings. Certain general principles, however, apply to every case, and if these are observed the details may vary indefinitely. First, the exercise must be regular and persistent ; second, it must involve not only certain muscles, but all the muscles of the body ; third, it must be sufficient in amount to produce an effect,—it should always, indeed, be carried as far as is possible without the production of exhaustion ; fourth, it must be sufficiently active to produce sweating, which, in many cases, may be encouraged by the use of warm clothing during exercise. Professional trainers, indeed, attach much importance to sweating as a means of reducing weight. It probably acts not only by dehydrating the body, but also by hastening the elimination of partially used-up materials, and is particularly indicated when there is any gouty tendency. In selecting the form of exercise care should be taken that it be as little irksome as possible to the patient, and if it can be made a pleasure much will be gained.

Bicycling offers an inexpensive and convenient means of muscular exertion, but has the disadvantage of not calling into play the muscles of the shoulders and arms. Golf seems to have an attraction for its devotees strong enough to make them forget that they are under "the doctor's orders." A travelling or hunting trip through the wilderness of the Rocky Mountains or the forests of Maine or Canada affords, as we can vouch for from personal experience, a most efficient, and to those who are willing to forego some of the luxuries of civilization a pleasant, method of reducing flesh.

A foot-exercise with whose fat-destroying tendency every trainer is familiar is running. The influence which it has upon heart and lungs does not differ from that of mountain-climbing, and, if there be any truth in the teachings of Oertel as to the value of pulmonic and cardiac gymnastics, running ought to be of especial value when the heart and lungs are giving evidences of being specially affected by the fat-accumulation. Boat-rowing, or even canoeing, may serve the purpose of the fat man. Wood-sawing is largely employed in some European anti-fat sanitariums, and is undoubtedly efficient. It can be very readily graduated by requiring one or two sticks more to be sawn each successive day. Gymnastic exercise, lifting of weights with pulleys, etc., may be employed, and even horseback-riding may be made efficient. Oertel further believes that mountain-climbing affords a method of gymnastically training the heart and lungs which may be of the greatest service in the treatment of a weak heart.

It must, however, be remembered that the heart is in an essentially different position from the voluntary muscle. The muscle loses its power through want of exercise, and is brought back from its soft, flaccid condition by exercise. Weakness of the heart-muscle, on the other hand, is practically never the result of lack of exercise of the heart, but is due to the accumulation of fat about the muscular fibres or to degeneration of the muscle, to exhaustion from overwork, or to the presence of some poison in the blood. If the cardiac weakness be connected with a fatty change in the muscle which is the result of general fatty infiltration of the body, the removal of such fat-infiltration will be accompanied by improvement of the muscle of the heart, which improvement may probably be aided by cardiac exertion. If, on the other hand, the cardiac weakness is the result of overstrain or of a true fatty degeneration, the probabilities are that it will be increased rather than diminished by cardiac exertion.

In all cases the exercise should at first be gentle and should be increased very carefully. Thus, mountain-climbers or runners should at first stop every few feet, to allow heart and lungs to recover themselves. Due regard must be had for the patient's general condition ; especially must it be remembered that the stout, flabby body is often associated with a weak heart-muscle which sudden severe exertion may easily overtax. Disregard of this fact has indeed occasionally led to a fatal result.

The fat of the body is chiefly if not exclusively derived from the hydrocarbons of the food. The notorious diet-list of Mr. Banting, which gave rise to the term "bantingism," was in no respect novel, but only conformed to the universally recognized principle that in corpulency withdrawal of carbohydrates from the food is necessary.

The extent to which the diet can be reduced depends, at least in the plethoric group of cases, almost entirely on the patient's strength of will. To accomplish any good the intake must self-evidently be less than the output,—that is, the demands of the system must never be satisfied, and the body must obtain the necessary force from the energy stored up in the fatty tissues. In short, the patient must undergo a mild form of starvation. The craving for food can be to some extent assuaged by the fat-free proteids ; but as these are insufficient for the needs of a healthy organism, no amount of them will entirely satisfy the appetite.

It is, therefore, plainly impossible to overcome the repugnance of patients to the diet by indefinitely increasing meat and other nitrogenous foods. Further, the excessive use of nitrogenous foods throws a strain upon the kidneys in requiring them to cast off an excessive amount of waste material ; and if in such cases there be a gouty diathesis there is danger of the production of arthritic symptoms.

No single dietary is suitable for all cases ; the practitioner should make a list in accordance with the circumstances of the individual case. In such list the actual weight of food to be taken should be given, as, without such check, the hungry man will always eat more than he believes he does. As samples we give, however, two dietary lists—the first is that of Banting ; the second, which was devised by Ebstein, has been much used in Germany, and seems to us the better of the two.

BANTING.

6 A.M. One pint of black coffee and one ounce of coarse brown bread or biscuit.

9 A.M. Four ounces of lean meat, three ounces of brown bread or biscuit, and half a pint of coffee.

2 P.M. Six ounces of lean meat, three ounces of brown bread or biscuit, six ounces of green vegetables, and half a pint of water, followed by half a pint of coffee.

6 P.M. Half a pint of coffee.

At supper two ounces of brown bread or biscuit, and a couple of glasses of sherry or claret. Fruit *ad libitum*, liquorice powder *pro re nata*.

EBSTEIN.

BREAKFAST.—Two hundred and fifty grammes of tea without sugar or milk; fifty grammes of white bread, with plenty of butter.

LUNCH.—Fatty soup, made from a marrow-bone; from one hundred and twenty to one hundred and eighty grammes of flesh, containing much fat; some vegetables; stewed fruit without sugar; two or three glasses of wine. Later in the afternoon, one cup of tea without milk or sugar.

EVENING.—One cup of tea without milk or sugar, thirty grammes each of bread and butter, one egg, or a piece of fat ham or fat roast meat, or cheese, and fresh fruit; no alcohol.

The following table, based upon the analysis of Carl Zahn, shows the comparative amounts of the different forms of food furnished by the rations of Banting and of Ebstein contrasted with the average normal:

	Albuminous Materials.	Fat.	Carbohydrates.
Normal	30. drachms.	25. drachms.	92. drachms.
Banting	25.5 drachms.	2. drachms.	5.25 drachms.
Ebstein	25.5 drachms.	21.25 drachms.	11.75 drachms.

As a foundation upon which the physician may arrange his bill of fare, the following table, originally compiled by Zahn, is appended. It gives the approximate amount of food-material in various common articles of diet in parts by weight.

Food.	Water.	Albumin.	Fat.	Hydrocarbons.
Mean of ten different kinds of simple soups . .	91.	1.1	1.5	5.7
Mean of ten rich soups	83.2	2.6	3.2	9.7
Boiled beef, lean, from young heifer	66.5	28.4	1.3	. .
Boiled beef, fat, from young heifer	49.	38.	12.1	. .
Beef from steers and oxen, boiled	56.8	34.2	7.5	0.4
Beef from steers and oxen, roasted . . .	59.	38.2	1.7	. .
Roast meats, including beefsteak, game, birds, etc., reckoned as an average	58.	38.2	2.7	. .
Veal, roasted	78.	15.3	5.2	. .
Fricasseed veal, with fat and milk	57.	22.3	10.4	10.
Fat roasted pork or goose	40.	34.6	24.2	. .
Smoked ham	59.73	25.08	8.11	. .
Boiled fish	74.20	22.10	0.60	0.70
Shell-fish	80.97	17.09	0.34	. .
Mean of seven different kinds of meat-foods . .	44.20	8.70	15.	28.9

Food.	Water.	Albumin.	Fat.	Hydrocarbons.
Potatoes, roasted	72.40	1.90	3.30	21.20
Potatoes, as salad	73.	2.10	3.20	21.80
Potatoes, boiled	70.	1.80	3.10	24.
Salad, green	94.2	1.40	2.	2.2
Vegetables in general, average	62.2	6.40	1.40	30.
White bread	40.45	6.15	0.44	51.12
Black bread	31.	11.	. .	57.
Dried fruit	1.18	13.31	3.18	81.08
Milk	87.42	3.41	3.65	4.81
Cream	65.51	3.61	26.75	3.52
Buttermilk	90.27	4.06	0.93	3.73
Butter	14.49	0.71	83.27	0.58
Cream cheese	35.50	17.44	40.80	5.21
Lard	0.70	0.26	99.04	. .
Sugar	2.16	0.35	. .	96.32
Vinegar	94.	. .	. .	0.4
One egg, estimated not by percentage, but by amount in average egg	8.25 ʒ	1.4 ʒ	1.35 ʒ	0.05 ʒ
Tea	97.9	0.3	. .	0.6
Coffee	94.7	0.18	0.52	1.4
Coffee with milk	93.3	1.60	2.20	1.6
Chocolate with milk	89.	3.7	3.6	3.8

It is the general custom to reduce the amount of water in the treatment of corpulent persons. This practice is apparently opposed to all our present knowledge of physiology ; it is impossible to see how water can increase the formation of fat, and theoretically it would seem that it should hasten the catabolic processes of the body. It may be, however, that empiricism has passed science, and that the common belief is correct, although we confess that we follow its beckoning with reluctance. Especially in those cases where there is a lithæmic tendency, as there usually is in the plethoric type of corpulence, the stoppage of water may do much harm by encouraging the retention of gouty poisons in the system.

LITHIASIS.

Although the gouty diathesis is one of the most frequent of bodily complaints in middle-aged persons of the upper class, and an enormous amount of study and research has been devoted to the determination of its dietetic treatment, yet no positive scientific knowlege exists for our theoretic guidance. This is the fault of the pathologist rather than of the therapeutist. The ultimate nature of the gouty diathesis remains as much unknown as the ultimate nature of syphilis. We are therefore forced to rely upon an unsatisfactory empiricism.

It would be very easy to quote contradictory statements from various clinicians of authority. In the brief space here possible it seems wisest to avoid both theoretic discussion and quotations from authorities, and we shall give simply our own views as based upon wide reading and very large experience in the treatment of gouty patients.

In the hygienic treatment of gouty patients it is essential that exercise

be taken systematically and with regularity. If circumstances permit, prolonged moderate exercise in the open air (such as may be obtained by horseback-riding, rowing, hunting, etc., or even by walking) is to be preferred. Gymnastic or house exercises may very well be substituted for this out-door work under special circumstances. The form is not a matter of much importance, provided the exercise involves the whole muscular system. The amount of exercise must be graduated to the needs of the individual case, different persons having no more the same measure of physical strength or the same needs for physical work than have different measures the same capacity. The endeavor must be always to push the exercise until it produces distinct physical weariness, and a better effect will usually be obtained if the exertion be sufficiently violent to cause free sweating. For the robust, hard muscular labor prolonged through many hours may be necessary ; while in the feeblest subjects it may be essential to begin with passive exercise associated with the least possible active exercise ; but day by day the physical exertion can be increased, and the results of systematic training in anæmic, feeble, gouty persons are sometimes astonishing.

Gouty patients may, for the purpose of dietetic discussion, be arranged in three classes : first, those who are robust and vigorous ; second, those who, with a distinct feebleness of constitution and sluggishness of habit, have a marked tendency to the accumulation of fat ; third, those whose nutrition and general vital forces are habitually on a low level.

In robust gouty persons it is essential that the quantity of food be lessened : such patients should be taught to rise habitually from the table with the appetite not thoroughly satisfied. In the second class of patients some control over the appetite is not rarely imperative, while in the third class of patients it is often equally essential to administer food beyond the cravings of the stomach. As individual cases occur grading all the forms of the gouty diathesis insensibly one into the other, the regulation of the quantity as well as of the quality of the food becomes a matter to be adjusted to the individual case. There are certain articles of food which should be denied to all gouty subjects. First of these in the list we would place cane sugar. The manifest effect of overindulgence in cane sugar in the lithæmic diathesis is probably not dependent upon any influence which it exerts on the general system, but upon the ease with which it undergoes fermentation in the alimentary canal and gives rise to acid products. Acid fruits, including the tomato and American strawberries, are also to be avoided by all gouty subjects, while non-acid fruits, if ripe, are often of great service and may be taken freely.

In gouty patients of the first class the albuminous principles of the food should be much decreased, but clinical experience proves that the form in which the albumin is taken is not unimportant. Red meats are especially to be denied ; white meats,—except pork,—fish, eggs, and milk are to form the main staples of animal food. Chicken is much preferable to turkey. Game is denied by most authorities, but we have

never seen any harm from its use. The waste muscle-products, such as kreatinin, xanthin, etc., have probably some connection with the injurious effects produced by red meats. If this be so, strong stock soups, which contain an abundance of these principles, ought to be injurious; and we have certainly known of violent attacks of gout apparently precipitated by the free use of beef tea, beef essence, and other similar stimulant liquids. If soups, therefore, are employed, they should be vegetable rather than stock soups. Ordinarily carbohydrates may be taken in moderation. Green vegetables, including roots, are especially serviceable.

The proper dietetic treatment of anæmic gouty subjects distinctly inclined to corpulence is a matter of difficult determination. The first thought would lead the physician to order a reduction in the habitual ingestion of albumin; but we have certainly known very good results produced in patients of this class by lessening very decidedly the carbohydrates in the food. When this is done, the albuminous ingestion must be increased rather than decreased, in order to support the system. In many of these cases, however, it will be found that the patient habitually takes an overplus of food, and much good may be achieved by lessening the quantity: in such patients the carbohydrates can be largely withdrawn and the habitual ingestion of albumin not increased. It is especially in patients of this class that the sagacity of the physician in modifying the diet to suit the needs of the individual will meet with reward. Our own plan has been in doubtful cases to make tentative alterations of the diet,—to regulate the quantity of food, withdraw carbohydrates, and order the albuminous nourishment to be taken chiefly in the form of fish, white meats, eggs, and milk. If the patient improve, the diet is evidently suitable for the individual case; if there be no improvement, or if there be aggravation, the diet should be at once altered.

In anæmic, impoverished, gouty subjects the best results are not rarely to be achieved by the employment of generous diet combined with the moderate use of alcoholic liquors. In selecting the drink, malt liquors and acid wines are to be avoided. Our own experience is that diluted spirits offer the best form for the administration of alcohol.

In any obstinate gouty case which fails to yield to the ordinary regulation of diet the so-called *milk diet* should be tried. It is not at present possible to give any sufficient scientific reason for the alterations which are occasionally produced in diseased human systems by the exclusive milk diet. The whole story of changes wrought by the milk diet in nutrition we do not know. It evidently, however, has a pronounced influence upon primary digestion in the intestinal tracts. It offers organic principles in so simple a form as to reduce to the minimum the labor of digestion, and probably to relieve greatly the hepatic and other similar glandular organs from excess of labor. By virtue of the large quantity of water it contains it enormously increases the flow of the urine and probably of the secretion of the skin, and in some cases is no doubt of great service in washing out excrementitious material from the body. Whatever may be the proper

scientific explanation of the fact, it is certain that in many cases of gouty diathesis and in various other abnormal conditions of nutrition an exclusive milk diet is extremely beneficial. Thus, in fatty anæmic subjects a course of two or three weeks of milk diet sometimes alters the nutrition so that afterwards feeding and tonics produce effects which were previously not attainable. We have always suspected that in these patients there is an underlying gouty diathesis. We have seen many cases of gouty disease of a chronic and subacute type in which remedial measures had entirely failed, but which yielded easily, though slowly, to an exclusive milk diet. Very frequently when it is simply intended to fatten the patient, or in the combating of the gouty diathesis, milk is given largely with other food; but to get the peculiar full effects of a milk diet it is essential that the patient abstain, at least for a time, from all other food. After two or three weeks oatmeal or cracked wheat or stale bread may be allowed, then green vegetables, and slowly the patient may thus be restored to ordinary diet. In severe cases, however, milk diet may be persisted in for weeks, and it is possible for the human adult to work laboriously and live exclusively upon milk. In order to afford sufficient nitrogenous nutriment, from five to seven pints of milk a day must be taken. This amount of milk contains too much fat for the needs of the system: it should therefore be skimmed. The so-called skimmed milk sold from creameries is, however, not suitable, because the fat has been too absolutely withdrawn from it, and because it is usually not so fresh as is desirable. The skimming of the milk should not be too close. It is essential that the milk be taken at intervals of not longer than two hours, and that it be drunk by sipping rather than by gulping, so as to avoid any danger from the formation of hard clots in the stomach. When the digestion is good the milk may be taken cold. When the digestion is very feeble it should be taken hot. But boiled milk should not be employed, as it is of more difficult digestion than is unboiled milk. During the progress of the milk course constipation is almost invariably present: this must be overcome by the administration of drugs. In gouty subjects saline laxatives are preferable.

CHAPTER III.

CALORIC.

THERE are two conditions of the force caloric, spoken of as distinct entities, but which are merely relative terms, expressive of the presence of an excess or of the absence of the normal amount, or, more strictly speaking, normal intensity of the force. Cold and heat, in connection with the human body, respectively mean an intensity of caloric below and above 98.5° F.

USE OF HEAT.

LOCAL USE OF HEAT.

The continuous application of moist heat acts as a relaxant to the surface of the body, producing probably a local congestion and exerting the influence of a slow counter-irritation. It is often practised with advantage in cases of sprains and internal inflammation.

The local use of an intense dry heat has recently been shown to be very advantageous in various local disorders of the limbs, and even of the trunkal muscles. For the purpose there are upon the market various forms of apparatus which agree in the general principle that the heat is chiefly applied by means of superheated air in a small chamber, with provision by means of ventilators and other devices for the removal of the moisture that comes from the skin. When proper care is exercised with an efficient apparatus the degree of heat that is borne without suffering is very remarkable. We have frequently carried the temperature up to 340° F. If, however, under these circumstances any moisture collects upon the surface of the part, blistering results. With most, if not all, forms of apparatus the parts should be lightly wrapped in patent lint. A temperature below 240° F. is rarely of service. In most cases, however, it is better to use in the beginning a lower temperature at one or two séances, partly for moral reasons and partly because the skin is often at first very sensitive, although it rapidly becomes accustomed to the higher temperatures. The duration of the application of the heat varies from ten to forty minutes.

We know of no experimental evidences as to the exact effect of this high temperature upon the affected joint. The fact, however, that the general bodily temperature may be raised three or even four degrees is evidence that there is a great absorption of heat, and that there probably is a local heating far above the highest fever point. Moreover, a distinct enlargement often occurs in the heated part, so that there must be an

excess of blood drawn to it. Probably both the circulation and the chemical movements in the joint are greatly accelerated. Certainly a remarkable absorption of exudates often occurs. We have frequently seen an acute attack of gout precipitated by the application to a long-diseased joint about which there was much exudation. This acute attack has often been accompanied by a very perceptible lessening of the exudate : we believe such attacks to be due to the absorption into the blood of gouty acids or salts which had been liberated from the tissues of the joint.

Although this method of treatment was first brought forward for the cure of *rheumatism*, there is *a priori* no reason for supposing that it can especially affect the general rheumatic condition, much less the rheumatic diathesis, unless the patient be well wrapped up in blankets and the local heat be used as a general sudorific measure, when whatever relief a free sweating can produce may be obtained. On the other hand, the method is of very great value in the treatment of local inflammatory conditions with exudation, whether these be or be not of rheumatic origin. In subacute and chronic *tænia synovitis*, in *chronic sprains*, in *acute sprains* when there is no severe acute inflammation or when this has been subdued by treatment, and in various forms of *synovitis* dry heat is of great service. Its effects are much more prompt and marked in cases of small than of large joints. Thus, it is much more serviceable when the ankle rather than the knee is affected, the result probably being due to the inability of the application to raise uniformly to a high point the temperature of a large joint. In rheumatic cases the method should be employed only as an aid to the general treatment of the condition.

GENERAL EMPLOYMENT OF HEAT.

The phenomena of death from cold show that a lack of caloric in the body is no less paralyzant of animal functions than is an excess of the same force. Evidently the organism was constructed to run upon a certain plane of heat, and cannot vary from this without serious results. By numerous experiments upon animals H. C. Wood has proved that in a cool apartment death rapidly results after section of the spinal cord, from falling of the bodily temperature, the animal which in a warm room will live indefinitely dying very shortly in a temperature of forty degrees. The cause of the inability of the animal to resist external cold after section of the cord is undoubtedly vaso-motor paralysis. Normally, the temperature of the interior of the body is maintained by keeping an outer layer of partially cooled tissue between the internal organs and tissues and the outer air. When the power of contracting the superficial vessels has been lost, the organism can no longer maintain this protecting layer, the surface-temperature rises to that of the interior, heat is rapidly lost, and the whole body is uniformly cooled.

Vaso-motor paralysis is produced by toxic doses of various remedies, and under these circumstances artificial maintenance of the bodily temperature is imperative, forming a very important portion of the treatment

of all such *poisoning*. *Collapse* from any cause is largely dependent upon, or, more correctly speaking, largely is, vaso-motor palsy ; hence in almost all forms of collapse the use of external heat is of great importance.

The late Charles Hunter very successfully applied this treatment to that form of collapse which follows injuries and surgical operations and is known by surgeons as *shock*. The lack of power of alcoholic and other ordinary stimulants in this condition is proverbial. The pathological state is undoubtedly vaso-motor palsy, the bodily temperature is much below normal, and the rational treatment consists in the hypodermic use of atropine and digitalis and the external employment of the hot bath. We believe this plan of treatment to be a most important addition to surgical therapeutics. In the first days of post-fœtal life the power of resisting external cold is very slight, and in many cases of still-born children, or of children whose vital powers are almost extinguished at birth, life may be saved by a high external temperature, the little waif being kept in an air of 98° F., and also away from the influence of cold walls and articles which would draw off, as it were, the slender store of heat provided by nature, radiation being greatly affected by the temperature of surrounding objects.

It is hardly necessary to dwell in greater detail upon the various forms of collapse. Enough has been said to illustrate the principle that, *whenever the bodily temperature falls below normal, pyretic treatment is demanded.* The vigor of the treatment should always be in direct proportion to the suddenness and extent of the fall of temperature.

In regard to the methods of applying heat, it must, in the first place, be understood that wrapping in blankets, etc., merely prevents cooling of the body, and when the animal temperature has already fallen it will not suffice at all. The same may be said of air heated to temperatures which can be readily obtained or can be continuously borne by the attendants. Radiated heat is somewhat better, and often the use of a brisk open fire is of service. The *hot bath* is, however, the only pyretic remedy that can be relied on. It should always be a full bath, in as warm a room as can be procured, and should be at a temperature of about 104° F. when the patient is put into it. The duration of the bath must vary with the circumstances of the case. It should not be less than half an hour, unless the mouth-temperature sooner become normal. During the bath the heat of the water should steadily be increased as fast as it can be borne if the patient be conscious, or, if he be unconscious, until a temperature of 110° F. is reached.

USE OF COLD.

LOCAL EMPLOYMENT OF COLD.

When cold is applied persistently to any part, it acts as a direct and very powerful depressant, of varying power according to its intensity. It is, therefore, used locally to reduce *inflammation*, especially when the

latter is of an active type. In this employment of cold, care must be exercised not to carry its use too far, lest it suspend all nutritive actions and interfere with those processes of repair which almost always form a part of inflammation. Indeed, it is possible to convert an inflammation into gangrene by the too energetic employment of this agency. Locally, cold is generally applied by means of cold-water compresses, irrigation with cold water, and the application of pounded ice, either enclosed in india-rubber bags or in bladders, or in the form of the *ice-poultice.** It is very doubtful whether the use of "freezing mixtures" is ever justifiable in inflammation. The effects of the cold in individual cases are to be judged of by the alterations in the heat and redness of the part. The local employment of cold belongs for the most part within the province of the surgeon, but the remedy is of great value in certain diseases. In *diphtheria* and in *anginose scarlatina* very great benefit may be obtained by enveloping the throat over the tonsils with powdered ice enclosed in bladders, in pieces of pigs' intestines such as are used by sausage-makers, or in thin india-rubber bags.

In internal trunkal inflammations, such as *pneumonia* and *pleurisy*, the application of cold by wet compresses or of ice-bags over the diseased organ has been employed extensively in Germany for many years, and has steadily maintained its reputation. It is especially serviceable when there is a tendency to general high temperature, and is probably even more useful in the catarrhal pneumonia of children than in adult cases.

In *meningitis* the great value of the application of ice to the shaven scalp is undeniable, and in *peritonitis* we have seen very great relief afforded by the use of cold, as recommended by Abercrombie, Niemeyer, and others. As is the case in pneumonia, warm poultices are more generally viewed with favor in peritonitis by the profession in this country. We have frequently used them with excellent effect, and in at least one instance after ice-poultices had been employed. In this case the cold applications were at first very agreeable to the patient, as were the warm poultices afterwards, and the good achieved seemed to be in accord with the sensations of the patient. It seems to us a good clinical rule to select the ice or the warm poultice according to the feelings of the patient. Early in the attack, when the fever is high, the ice will generally be the more useful.

In using cold for the purpose of combating inflammation, the application must be kept up until the desired effect is produced. When employed intermittently, cold even becomes a stimulant, the reaction which follows its first impression being greater than its direct effects. Hence the cold douche has been used with asserted advantage as a stimulus to *sluggish ulcers.*

It seems proper here to direct attention to the statements of Fr. Mosler,[1] that the application of cold water to the abdomen produces contraction of the spleen, and that the cold douche applied for two or three

* Made by mixing finely broken ice with dry Indian meal or fine sawdust.

minutes and repeated at longer or shorter intervals very sensibly affects the enlarged spleen of intermittent or typhoid fever, and even of such chronic diseases as leukæmia, in which class of cases the application should usually be made twice a day.

COLD AS A TONIC AND STIMULANT.

Almost every one has experienced the exhilaration of the reaction which, in a healthy person, follows the sudden dash of a cold shower-bath or the plunge into a mass of cold water. The researches of Liebermeister, which will be detailed hereafter, prove that a cold bath, when of not too long duration, actually increases the oxidation of tissue to such a degree as to elevate the temperature of the body. When cold bathing is employed as a tonic, the first principle to be borne in mind is that the bath should not be too severe or too long continued, else it becomes a direct depressant, debilitating and lowering the temperature of the bather. When the subject has sufficient vital power to react after the bath, sea-bathing is often of very great service, but in debilitated persons it may produce serious exhaustion, partly by the fatigue induced and partly by the excessive abstraction of heat from the body. The cold bath, when not followed by a healthy reaction, is anything but a tonic.

COLD IN PYREXIA.

The use of cold in fever is no new thing : employed by Galen, used not infrequently during the last century, first systematized and insisted upon by Currie, cold bathing in fever was brought before the world as a really new-born measure by Brandt, of Stettin, and received the seal of permanent usefulness from the scientific clinical labors of Jürgensen at Kiel.

The consideration of the method naturally divides itself into,—first, a study of its physiological action ; secondly, an investigation as to its clinical value ; and thirdly, a more particular account of its effect, the cases to which it is best adapted, and the method of its application. Moreover, there are two distinct forms of pyrexia, which may be termed the acute and the chronic, and which are best considered separately.

Acute Pyrexia.—If the following propositions be true, caloric in excess acts as a direct poison to the body, and the phenomena of severe acute fever are largely due to the heat itself. The proofs of the propositions are given very briefly after them.*

First. External heat applied to the body of the normal animal, so as to elevate the temperature, produces derangements of the nervous system, of the circulation, etc., precisely similar to those seen in natural fever, the intensity of the disturbance being directly proportionate to the rise in temperature.

Second. Heat applied locally to the brain or to the heart produces in

* Want of space prevents the elaboration of this. The unconvinced reader is respectfully referred to the treatise of H. C. Wood on Thermic Fever, and his Toner Lecture on Fever.

the functions of the organ those disturbances which are familiar phenomena of fever, the intensity of the disturbance being directly proportionate to the excess of heat in the organ.

Third. The withdrawal of the excess of heat in fever is followed by a relief of the nervous and circulatory disturbances.

When a dog, cat, or rabbit is shut up in a box, as in the experiments of H. C. Wood, heated either by the sun's rays or by artificial means, the temperature of the animal rises, and at the same time the pulse-rate becomes *pari passu* more rapid, the breathing grows more and more hurried, and the restless, uneasy movements of the victim show the general distress it is suffering. As the temperature increases, the nervous disturbance becomes more and more apparent; and stupor, coma, partial paralysis, convulsions, and finally death by arrest of the respiration occur. These phenomena sometimes come on gradually, but sometimes are developed suddenly. The temperature at which death occurred in these experiments varied in the rabbit from 111° to 114.5° F.; in the dog it was about 111° F. In man a similar series of phenomena are developed by exposure to excessive heat, although, owing to his extraordinary power of cooling his body and of protecting it against cold, he is able to bear extremes of temperature far beyond the points which would prove fatal to any given species of animals. Yet when his body is heated the results are the same, as is proved by the terrible mortality of sunstroke.

"To prove the second proposition, I" [H. C. Wood] "caused hot water to flow through pigs' bladders fitted as a sort of bonnet to the heads of cats and rabbits. It is evident that with small animals we can in this way heat the brain without heating materially the remainder of the body. It was found that coma, with or without convulsions, was produced. Sometimes the stupor came on gradually, hebetude slowly deepening into coma, but in other instances unconsciousness was developed very suddenly. It was also found that severe nervous symptoms and death were produced when the brain reached the temperature which was fatal to the animal in the hot box. Without occupying more space, the conjoint labors of Lauder Brunton and Liebermeister have proved that the accelerated pulse in fever is largely due to the action of the heat upon the heart and its nerves: so that the second proposition may be considered demonstrated.

"In regard to the third proposition, I have frequently taken animals out of the hot box perfectly unconscious and plunged them into a bucket of cold water, have watched the temperature of the water rise while that of the animal fell, and as the bodily heat came towards normal have seen the coma disappear, so that within ten minutes the at first absolutely comatose and dying rabbit would be skipping about on the grass. I have placed a man whose temperature was nearly 110° F., who was unconscious, with a feeble running pulse of 160 or 170, irregular, jerking, slow respirations, and every indication of immediate death, in a bath of 60° F., and within a minute and a half have seen consciousness partially restored, and in another minute and a half the man trying to get out of the bath. What

could the bath do to affect the man so profoundly and so quickly but withdraw the heat? That the heat was present, and that it was withdrawn, the thermometer proved. If the drowsiness had been due to simple congestion of the brain, very certainly would the bath, by driving the blood from the surface, have increased the trouble. It must be borne in mind that this case is by no means unparalleled: similar instances of the good effects of the sudden withdrawal of heat in rheumatic hyperpyrexia have been recorded by both English and German observers, and recent Continental literature is full of reports of the relief of nervous symptoms in various pyrexias by the abstraction of heat.

"Finally, as excessive heat is present in fever, as excessive heat, when present, is not only able, but is forced, so to speak, by its own attributes, to produce disturbance of the functions of innervation and circulation, and as the withdrawal of the excessive heat in fever is followed by instantaneous relief of the symptoms of disturbed innervation and circulation, surely the conclusion is logically inevitable that excessive temperature is the chief cause of the other symptoms of fever, and that in *acute pyrexia* threatening life the heat should be withdrawn as rapidly as possible by means of the cold bath."

Chronic Pyrexia.—The effects of a long-continued pyrexia, not sufficiently intense to induce immediate serious symptoms, upon the structure of the various tissues have been elaborately investigated by Liebermeister,[2] who found that the liver, spleen, kidneys, voluntary and involuntary muscles, blood-vessels, and even the nerve-centres undergo a granular degeneration during the continued pyrexia. The lesion was constantly present in the bodies of those who had suffered in this way during life, entirely independently of the nature of the primary disease. In cases of infectious fever in which the temperature had never been high, this granular degeneration did not exist. Previous to the investigation of Liebermeister, Zenker had demonstrated that the muscles undergo a peculiar granular degeneration in typhoid and other fevers; and the fact has been abundantly attested by later observers. We do not know that the observations of Liebermeister as to the occurrence of this lesion in non-infectious pyrexia have been confirmed, but we have no doubt of their correctness.

It is evident that in all fevers a primary therapeutic indication is to reduce the temperature. Of course, if possible, this should be done by checking the excessive production of heat; but, unfortunately, this often lies out of our power, and we are forced to abstract the heat by mechanical means.

It is *a priori* impossible to determine what effect upon the production of heat the rapid abstraction of it would have, but, from the well-known powers of the organism to resist external cold, it seems probable that the heat-production would be increased rather than diminished by the abstraction of caloric. An experimental study of this problem has been made by several observers, but with, unfortunately, different results. Weisflog[3] has found that the local abstraction of heat by a cold sitz-bath causes a rise in the temperature of the axilla, and that in fever-patients,

unless the sitz-bath is prolonged over twenty-minutes, no fall of the bodily temperature results. In 1860 Kernig[4] found that a healthy man in a bath of the temperature of from 28° to 30° C. produces about twice as much heat as normal; in a bath of 24° C., about three times as much; and in a bath of 20° C., about four times as much. Liebermeister[5] found that in a healthy man exposure to cold for a brief period of time causes a rise in the bodily temperature, and on extending his researches into fever proved that where the external cooling was not too powerful or too long continued the same was true of fever-patients. From this it follows that the use of external cold stimulates heat-production. This, to our minds, has been confirmed by the chemical researches of J. Gildemeister,[6] of Lehmann,[7] and of Liebermeister[8] himself upon men, and by those of A. Roehrig and N. Zuntz[9] upon animals, all of which show that both in health and in fever very much more carbonic acid than normal is eliminated under exposure to cold. This would appear to prove that cold baths increase the production of animal heat. It seems most probable that this is the case; but A. Murri believes that he has proved that the cold baths have no such influence.* At any rate, the investigations of Liebermeister and others have shown that the first rise of temperature produced alike in healthy and in fever subjects by exposure to a moderate and not too long continued cold is followed after removal of the cold by a fall of bodily temperature of greater or less degree. While, therefore, external cold probably first stimulates, it afterwards depresses the production of animal heat. The further experiments of Liebermeister[8] upon the elimination of carbonic acid are also in accord with his temperature-study, for he found that after the bath the elimination sank below normal, and so continued for a considerable period.

If the cold bath really affects the fever-process, it ought distinctly to reduce the excretion of urea. That it has this action would seem to be proved by the research of Sassetzky,[10] who found that the continuous use of the cold bath invariably lessened the urinary elimination of nitrogenous material and of the phosphates, although it increased the total flow of urine. The subject is, however, a very difficult one, chiefly because it is almost impossible to know in any individual case what the elimination of urea would have been if no baths had been used. Bauer and Künstle[11] gave to the patients cold baths upon alternate days, and found that the excretion of urea was in each case greater on the days when baths were used than on those on which they were not employed. These experiments have been quoted as showing that the cold bath increases the excretion of urea, but in Schleich's[12] investigations on the effects of hot baths the increase of the excretion of urea frequently did not show itself until the day after the bath. It is probable, therefore, as believed by Schleich, that the destruction of albuminous substance in the tissues is

* We have never seen the brochure of A. Murri (*Del Potere regulatore della Temperatura animale*, Firenze, 1873). It is abstracted in the *London Medical Record*, vol. i.

not manifested in urea-elimination until after twenty-four hours, or, in other words, that twenty-four hours are necessary for the completion of the formation and the excretion of urea: so that if the baths are used, for example, on Monday the urinary solids will indicate their effects not on the same day but on Tuesday. If this be correct, the experiments of Bauer and Künstle are in accord with those of Sassetzky in showing that the cold bath lessens the formation of urea in fever.

During the bath the pulse of the fever-patient usually becomes much smaller and harder, and the sphygmographic tracings made by Winternitz before and after the use of the cold bath (if tracings of this kind can be trusted) indicate that there is after the cold bath greatly increased arterial tonus. (See *Verhandl. des Congr. für Innere Med.*, 1886.) It may be that the good obtained by the cold bath is really due to a reflex action upon the nerve-centres, and is not entirely the result of the withdrawal of the heat.*

The results of the physiological study of the effects of cold in fever may be summed up as follows. *During a sufficiently prolonged application of cold the bodily temperature falls, although an increased production of heat*—i.e., *consumption of tissue—at first occurs. After the application, the bodily temperature continues to fall, or but slowly regains its former position: the present evidence at our disposal indicates, but is not sufficient to prove, that this slow regaining of bodily temperature is due to a diminished production of animal heat,—that is, to a decrease in the waste of tissue and in the formation of urea and carbonic acid.*

When the use of cold in fever was first recommended in this work the method was looked upon with disfavor by so many medical practitioners, especially in the United States, that it seemed necessary to discuss, carefully and in detail, the statistics of the subject to show that these were sufficiently large to be decisive, and were sufficiently plain in their teaching

* Naunyn (*Archiv f. Exper. Path. und Pharm.*, 1884, Bd. xviii., Heft 1 and 2), indeed, denies that the good achieved is due to withdrawal of heat at all. In his experiments he found that if he maintained proper ventilation, carefully giving food and water, he could *gradually* heat rabbits up to the temperature of 107° and 108° F., and keep them at this temperature for weeks without their evidencing any inconvenience and without the production of any internal lesions. Krishaber was also able to maintain in a dry room 117° F., his own temperature reaching 107°, pulse 85, respiration 35. Naunyn, as the result of his experience, is a very strong advocate of the employment of frequent baths in the treatment of fever, but believes that they act by indirectly reducing bodily waste and increasing renal secretion, strengthening the pulse, and stimulating the nerve-centres. L. Schweinburg and C. Pollak (*Centralbl. f. Gesam. Therap.*, March, 1887) have found in a series of apparently very careful experiments that cold hip-baths notably increase blood-pressure and lessen pulse-rate, while hot hip-baths have the opposite effect. Naunyn believes that better results are obtained from the use of constant lukewarm baths than from the employment of excessively cold baths. In very severe cases, marked by dicrotic pulse and disturbance of the sensorium, the bath treatment, according to Naunyn, should be commenced before the axillary temperature reaches 103° F., and frequently a warm bath may in such case be given between two cold baths. Such a treatment is especially indicated when there is marked delirium, tremor, subsultus tendinum, or great restlessness; a warm bath in the evening then seldom fails to produce some favorable result.

to demonstrate the value of the practice. As, however, at present almost all medical authorities are in accord in recommending the early use of cold in pyrexia, we have omitted from the present edition these statistics, and would refer any doubtful student to the ninth edition of this work, page 63.

The cold-water treatment has been employed upon a large scale, especially in *typhus* and *typhoid fevers*, but there can be no doubt of its value in *scarlet fever*, in *diphtheria*, *septicæmia*, and other germ diseases accompanied by high bodily temperature. In diphtheria or anginose scarlatina the general use of cold may often with great advantage be combined with a local application of the ice-bag or the ice-poultice to the throat. During the summer months *serous diarrhœa* (*cholera infantum*), in some of its forms, annually destroys large numbers of children in this country. In most of these cases the bodily temperature is, first or last, much elevated, and the diarrhœa is produced and maintained by the heat, as originally pointed out by Comegys.[13] All the ordinary methods of drug-administration frequently fail, or, at most, succeed only in keeping the child alive until the heat of the weather subsides. Under these circumstances, antipyretic treatment acts in a magical manner. Usually simple bathing in water of about 75° F., at intervals of from three to six hours, will be found sufficient, but in some cases the plan recommended by Comegys may be required,—namely, cold affusions while the child is sitting in a cold bath. The effect is usually immediate, quiet and sleep at once replacing the wakeful restlessness so distressing to mother and child. There may be a few instances of sudden collapse with low temperature from exhaustion by the serous discharges, but usually cases in which the disease is said to "go to the head" are those in which the temperature rises so high as to produce brain-symptoms ; under these circumstances the vigorous use of external cold is imperatively demanded.

The high temperature that prevails in sthenic *pneumonia* would appear urgently to demand the abstraction of heat, and, although the prejudices of the profession and the laity were in the beginning strongly opposed to the use of the cold bath in pulmonary inflammation, gradually the method has come into practice. Liebermeister, in one of his early publications, stated that whilst in six hundred and ninety-two cases of pneumonia treated in the hospital of Basel in various ways the mortality was 25.3 per cent., in two hundred and thirty cases treated in the same hospital by the thorough antipyretic method the mortality was only 16.5 per cent., and there can be no doubt that in properly selected cases bathing does great good.

It must, however, be remembered that a moderate pyrexia does not do great harm to the system unless it continues for a length of time, and hence in those diseases which, like pneumonia, last but a few days the reduction of temperature is not so important as in affections in which the fever is of long continuance. Thus, a temperature of 103° F. may be disregarded in a short pyrexia, whereas in a typhoid fever it would call imperatively for the use of external cold. Further, in acute internal inflammations the temperature can very frequently be reduced with ad-

vantage by the local application of cold ; thus, in *pneumonia* cold compresses to the chest may be employed ; in *dysentery* the free use of ice suppositories and of large injections of ice-cold water is often of the greatest service, both by the local and general influence.

It being acknowledged that in cases with long-continued pyrexia the external use of cold is a much safer and more efficient means of reducing the temperature than are antipyretic drugs, the practical question presents itself as to what are the contra-indications to the use of cold in typhoid and other allied fevers.

According to ideas formerly held, bronchitis and pneumonia would especially seem to be in the way. The serious lung affections of low fevers are, however, chiefly dependent upon the general adynamia, which is in turn largely the result of the excessive temperature ; and we have no doubt of the correctness of the assertion made by Liebermeister, that in the exanthematous fevers " pneumonia, hypostatic congestion, and the like offer no reason for suspending the baths ; the hypostatic troubles sometimes disappear under their use." If in the beginning of a typhoid fever a severe *bronchitis* or *pneumonia* arise without great elevation of temperature, some hesitation may properly be felt in producing active antipyresis with cold. If, however, the symptoms occur late in the fever they do not contra-indicate the use of the bath ; and even early in the fever, if the pyrexia be severe, balneal measures should be practised.

Liebermeister affirms that *perforation of* or *hemorrhage from the bowels* is a contra-indication to the use of cold in typhoid fever, because cold has a tendency to produce determination of blood to the internal organs. The experience of Wunderlich[14] is, however, very much opposed to this idea of Liebermeister's. He treated sixteen typhoid cases of severe intestinal hemorrhage with cold baths, with but two deaths, neither of which resulted directly from the hemorrhage, one being from intestinal perforation and one from severe pneumonia. This mortality is certainly a very small one, for when cold water was not employed, out of thirty-two cases Griesinger had ten deaths ; out of twenty-one, Jenner lost seven ; out of fourteen, Gietl lost six ; and Jaccoud[15] had six deaths in six cases. Bauer,[16] however, is in agreement with Liebermeister in believing that the baths should be discontinued during intestinal hemorrhage. Yet their views seem to be based upon preconceived theory rather than upon actual trial. The proportion of cases in which intestinal hemorrhage occurs does not seem to be increased by the cold-water treatment ; at least Golsdammer[17] states that under the older methods thirteen thousand five hundred and sixty-three cases gave five hundred and thirty of intestinal hemorrhage, while five thousand six hundred and thirty-six cases of cold-water treatment yielded two hundred and forty of intestinal hemorrhage, the percentage being in the two cases respectively 3.9 and 4.2. Menstruation is not a contra-indication. Brandt appears to consider any contra-indication to the use of the cold bath in typhus fever a myth, and the drift of the testimony is such that *no local internal* disease except feeble heart

ought to be considered as absolutely contra-indicating the use of cold baths when the temperature is high in typhus or typhoid fever.

It is otherwise when there is a general tendency to collapse,—when the heart is so weak that local stases of blood occur in almost all the internal organs. Under these circumstances the circulation has not sufficient power thoroughly to equalize animal heat, so that it is possible to cool the exterior of the body several degrees without materially affecting the temperature of the interior.

Moreover, the first effect of cold water upon the surface of the body is to drive blood into the interior, and if the heart be excessively feeble there is grave danger of severe internal congestion, and even of paralysis of a feeble right heart. The great contra-indication to the use of external cold is, therefore, *profound adynamia* or *excessive heart weakness*. Whenever there is any doubt in the practitioner's mind upon this score in an individual case, the attempt should be made to reduce the temperature within bounds by immersion in tepid water.

In carrying out the antipyretic treatment of fever certain general considerations should never be forgotten. So long as the temperature of the body remains distinctly above the normal there is no danger of any patient taking cold. The fall of the bodily temperature may continue after the removal of the patient from the bath ; hence it is important that the patient be taken out of the bath so soon as the temperature reaches 100.5° F. The temperature at which the bathing should be commenced varies with the probable length of the pyrexia ; in typhoid fever we would put the limit at 102.5° F. in the mouth. As it is possible to cool the axilla without cooling the interior of the body, all temperatures should be taken in the mouth or the rectum. The object of the bath is a reduction of the temperature, and unless this is effected no good results. On the other hand, it is always of importance to avoid, as far as may be, shock, discomfort, or the possibility of overdoing the heat-reduction ; hence the rule in the choice of the methods of cooling the body to employ that which will accomplish the desired effect with the least disturbance.

Rarely in the adult, more frequently in the child, free sponging of the exposed body with cold water and alcohol will suffice. Next in power comes the cold pack, in which the naked patient is wrapped in a sheet dripping with ice-water, left uncovered save by the sheet, and sponged with cold water from time to time. Next is the tepid bath, 90° F. ; then the tepid bath cooled, whilst the patient is in it, by the addition of cold water or of pieces of ice. Some prefer to put the patient directly into water of 75° F., but the gradual cooling of the bath seems to us preferable. When a portable bath-tub can be brought to the bedside of the patient and readily filled and emptied, its use is accompanied by less fatigue and disturbance than are any other efficient means of employing cold. The patient, wrapped in a sheet, is to be *lifted* into the bath by two attendants, and then made comfortable with pillows, etc. Unless the pyrexia be very severe, the bath should be at a temperature of 90° F. and

cooled down *pro re nata*. When no portable bath-tub is at hand, efficient antipyresis may be had by lifting the patient, wrapped in a sheet, upon a cot covered with a rubber blanket, and sousing rather than sponging him with cold water from a large carriage-sponge. If the sacking-bottom or the canvas of the cot be so loose as to sag down several inches, and the rubber blanket be turned up at the bottom and top over a wide board nailed across the top and bottom, the patient during the sponging lies in a big pool of water, and all the effect of the cold bath is obtained by removing with a carriage-sponge this water as fast as heated, and sousing fresh cold water (ice-water, if necessary) freely over the upper part of the patient. Sometimes the bed in which the patient lies can be arranged with a rubber sheet drawn up over the pillow and down over the foot, folded into a trough, and the cold water applied without wetting the bed.

During the bath the hands should be kept out of the water, and the surface of the body should be briskly rubbed so as to divert the attention of the patient, and also to prevent as far as may be the driving of the blood from the surface of the body by the local effects of the cold. When the circulation is weak, advantage is often gained by putting the feet or even both feet and hands upon a hot-water bag.

The temperature of a fever patient should during the treatment be taken every three or four hours. Theoretically the bath should be repeated whenever the temperature gets above the limit, 102.5° F., but practically it is best not to use the bath oftener than once every three or four hours. It should be administered if required during the night as well as during the day, and its use should not be allowed to interfere with any other treatment which may be indicated.

In explaining the use of the method to the patient or friends, it must not be forgotten that the cold bath in typhoid fever and other acute diseases associated with high pyrexia does not arrest the disease-processes; and, whilst it may greatly lessen the mortality, it shortens the duration of the disease only in so far as it prevents complications. On the other hand, the disease-processes do not exhaust the patient so much as when the fever is allowed to continue unchecked, so that convalescence is usually much more rapid than under the older plan of treatment. By the antipyretic treatment the intense prostration, delirium, stupor, carphologia, involuntary passages, and other manifestations of the typhoid state are greatly lessened.

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CHAPTER IV.

ELECTRICITY.

GENERAL CONSIDERATIONS.—Electricity is a force which is developed in various ways, but which is essentially the same entity under all circumstances. When it is obtained by rubbing two surfaces together, it is known as frictional electricity; when it is obtained by the union of two dissimilar metals, it is called galvanism. Frictional electricity is almost never used in medical practice, and we shall say nothing more about it in this book.

FIG. 1.

There are a large number of different patterns or arrangements of the elements which generate galvanism, but the ideal or typical cell may be said to be formed of two dissimilar metals immersed in some corrosive liquid and connected with each other by a piece of wire externally. Under these circumstances the current starts from the metal most easily corroded, passing through the liquid to that less easily acted upon, and from this over the external wire to the starting-point. The external end of the least easily corroded plate is therefore always giving off electricity, and is known as the + or positive pole, while the corresponding end of the other plate is constantly receiving electricity, and is spoken of as the — or negative pole. When wires are attached to these plates they become, as it were, prolongations of the plates, and their ends constitute the poles. Thus, in the diagram, C = copper, Z = zinc, P and N = poles, and the arrows show the direction of the current. The positive pole is called the *anode* (ἀνά, upward, and ὁδός, a way); the negative, the *cathode* (κατά, downward, and ὁδός).

As the electric current does not primarily exist, it is evident that in the typical or ideal galvanic cell there must be something which sets it in motion. This force is the so-called electro-motor force, and has been determined by physicists to be a definite quantity for the same combination of metals at the one temperature. This force is generated at the point of contact of the metals, in obedience to the law discovered by Volta, that when two metals are in contact with each other a disturbance of the electrical conditions of those metals occurs. The amount and energy of this disturbance vary according to the nature of the metals, and experiments have shown that all metals have definite electro-motor powers or properties, and that they can readily be arranged in a regular series.

A study of this series is not necessary to an understanding of electro-therapeutics, and the reader desirous of knowledge upon this especial point is referred to works on physics. It must be borne in mind that the electro-motor force is constant, so that in any given combination of metals in a galvanic cell the electro-motor force is always the same, whether the plates of the metal be large or small, whether the solution be an acid, a saline, or pure water. The strength of the current is not, however, decided entirely by the electro-motor force of the cell. Every known substance refuses more or less imperiously to allow the passage of electricity. The best conductors oppose a really very great resistance. Now, it is evident that this resistance is opposed to the electro-motor force, and that if it be greater than the latter it will altogether prevent the passage of any current. The strength of the current, then, depends upon the relation between the resistance and the electro-motor force ; and we have the celebrated law of Ohm, which may be expressed by the formula $c\ (current\text{-}strength) = \frac{e\ (electro\text{-}motor\ force)}{r\ (resistance)}$. This law experiment has shown to be imperative, no increase or diminution of the size of the plates, no change in the character of the solution, affecting it.

The resistance to the current in a galvanic combination is a double one : inside of the cell the fluid between the plates opposes the passage of the electricity, and outside of the cell the conductor which completes the circuit also offers a resistance. The reason a battery almost ceases to yield a current when water is substituted for the acid usually employed is not a purely chemical one, but simply because water is an almost complete non-conductor, and offers triumphant resistance to the current, while the acid conducts and readily allows the current to pass. The entire resistance (r) is then made up of two factors : the internal resistance (ir), and the external resistance (er). The formula of Ohm may therefore be read $c = \frac{e}{ir + er}$.

As already stated, when the plates of a cell are increased in size the electro-motor force is not increased, but as the surfaces of the plates are increased the diameter of the conductor—*i.e.*, the transverse section of the fluids between the plates—is increased ; and consequently, as the resistance in a conductor is inversely as the size of its cross-section, the strength of the current is increased. To make this a little clearer, suppose ir in a certain cell equal 10, then $c = \frac{e}{10 + er}$; if now the plates of the cell be doubled in size, $c = \frac{e}{\frac{10}{2} + er} = \frac{e}{5 + er}$. A similar result—*i.e.*, lessening of the internal resistance—can be achieved by shortening the distance between the plates of the cell,—*i.e.*, the length of the conductor, —or by in any way making the intervening liquid a better conductor.

The change in strength of a current by the increase of the size of the plates of the cells can readily be expressed by the formula of Ohm.

If the letters signify as before, and the internal resistance be diminished y times by increasing the size of the plate y times, instead of $c = \frac{e}{ir + er}$ c will $= \frac{e}{\frac{ir}{y} + er}$. If, instead of a single cell, a number of cells are arranged in such a way that the copper of one is connected with the zinc of the next, the electro-motor force of the combination is equal to the sum of the electro-motor force of all the cells: thus, if $e =$ the electro-motor force of the single cell, and $y =$ the number of cells, the electro-motor force of the battery will be ye. It is plain that the internal resistance of the battery is also increased y times, so that the formula of Ohm will stand $c = \frac{ye}{yir + er}$.

Of course the strength of a current is greatly affected by the external resistance. In very many instances the external resistance is enormous. Suppose, then, that this external resistance in a given case be 1000 times the internal resistance, the formula of Ohm will read, $c = \frac{e}{ir + 1000\ ir}$. It is evident that under these circumstances ir, the internal resistance, becomes very insignificant, and that very little is gained by increasing the size of the plates,—*i.e.*, by diminishing the internal resistance; for if the plates were increased fivefold, the increase of the strength of the current would only be the difference between $\frac{e}{\frac{ir}{5} + 1000\ ir}$ and $\frac{e}{ir + 1000\ ir}$, a difference which is very slight. On the other hand, when the external resistance is very great, everything is gained by increasing the number of cells,—*i.e.*, increasing the electro-motor power; for $\frac{5\ e}{5\ ir + 1000\ ir}$ gives a very different result from $\frac{e}{ir + 1000\ ir}$. When, therefore, the *external resistance is many times greater than the internal, practically nothing is gained by increasing the size of the plates, everything by increasing the number of the elements.*

The converse of the above reasoning also holds. If the external resistance be very slight, the internal rises in importance. Thus, suppose $er = \frac{ir}{1000}$. Then the formula would be $c = \frac{e}{ir + \frac{ir}{1000}}$. In this case a great deal is gained by increasing the size of the plates, for $\frac{e}{\frac{ir}{5} + \frac{ir}{1000}}$ gives a very different result from $\frac{e}{ir + \frac{ir}{1000}}$. In such a case, by quintupling the size of the plates the strength of the current is practically increased fivefold. On the other hand, it is plain that when the external resistance is slight the gain by increasing the number of cells is a slight one, for the internal resistance is increased as many times

as the electro-motor force. Thus, if five cells are used, the formula will be $c = \frac{5e}{5ir + \frac{ir}{1000}}$, which will, of course, give practically the same result as $\frac{e}{ir + \frac{ir}{1000}}$.

The law, then, may be stated to be that when the *external resistance is very slight, increasing the number of the elements has no practical effect upon the strength of the current, while an increase of the size of the elements has the greatest effect.*

When there is *no very great disproportion between the internal and the external resistance, it is evident that the strength of the current may be increased by increasing either the size or the number of the elements.* Thus, if $er = ir$, $c = \frac{e}{ir + er} = \frac{e}{ir + ir}$; and increasing the size of the plates fourfold will give the formula $c = \frac{e}{\frac{ir}{4} + ir}$; or increasing the number of the elements to four will yield the formula $c = \frac{4e}{4ir + ir}$. Perhaps the result will be clearer if figures be used. Suppose $e = 100$, $ir = 10$, and $er = 10$. Then the first formula will be $c = \frac{100}{10 + 10} = 5$; the second, $c = \frac{100}{\frac{10}{4} + 10} = 8$; the third, $c = \frac{400}{40 + 10} = 8$. When, therefore, the *external and the internal resistance are equally balanced, the strength of the current is equally increased by increasing either the number or the size of the plates.*

The application of the foregoing principles to electro-therapeutics is a very simple one. In the ordinary applications of electricity to the body the resistance of the tissues is very many times greater than the internal resistance of any battery, and consequently the latter may be totally disregarded. Hence for ordinary purposes the formula stands $c = \frac{e}{er}$, and power can be gained only by increasing e,—that is, by augmenting the number of cells.

When, however, it is desired to act upon the blood in an aneurismal sac, the needles are brought close to each other; and, moreover, the blood is a comparatively good conductor of electricity. Hence in such cases the external resistance is so much reduced that the internal becomes of such importance that it should not be overlooked. It follows, therefore, that when an aneurism is to be acted upon the plates should be increased in size, while at the same time a number of cells should be used.

In the so-called "galvano-cautery" the current is not passed through the body at all, but through a wire, which is thus kept at a white heat. In this case the external resistance is vastly less than when human tissues form a part of the circuit. Hence it becomes a matter of importance to reduce to as great a degree as possible the internal resistance, and the elements or plates should be very large and should be placed very close to one another in the cells. The external resistance is not, however, so slight that it can be entirely overlooked, and hence a number of cells are combined with one another, so as to give sufficient electro-motor force.

In writing or speaking about the use of electricity in medicine, it is a matter of great importance to avoid the use of the old terms *quantity* and *intensity*, which, to use the language of an eminent writer on galvanism, "are remnants of an erroneous theory." The amount of mystification which has been produced by talk concerning the therapeutic effects of currents of large quantity with low intensity as contrasted with those of currents of high intensity and small quantity is equalled only by the amount of nonsense which has been written. Currents of galvanism have really only one attribute,—*i.e.*, current-strength,—and that is in strict accordance with the law of Ohm.

If $c = \frac{e}{r}$ it is evident that, in order to have a unit by which there can be a measurement of an electric current, it is necessary to have a unit of resistance and a unit of electro-motor force. The unit which has been finally settled upon by electricians as the measure of electro-motor force is known as a *volt*. It is equivalent to 10^8 (10 raised to its eighth power) absolute French units of force.* The unit of resistance is termed an *ohm*, and equals 10^9 absolute French units. Substituting these units for their representative letters in the formula $c = \frac{e}{r}$, we get $c = \frac{1\ volt}{1\ ohm}$. In this way the unit of current-strength is obtained, and is known as an *ampère*. This unit is, however, entirely too large for practical purposes. It is therefore generally substituted by the so-called milliampère, which is the one-thousandth part of an ampère, or $\frac{1\ volt}{1000\ ohms}$. The term galvanometer has long been used in electricity as the name of an instrument which shows the existence of an electro-current. An absolute galvanometer is one which reveals not only the current, but also the amount of electricity that is passing. As good absolute galvanometers are now manufactured which measure the current in milliampères, it would seem at first to be

* All forces are convertible into one another, and hence it is possible to refer the unit which is employed in measuring electricity, heat, or other force to what is known as the absolute unit of force. The absolute unit of force is always mechanical, and has in the past varied in different countries. At present, however, scientists almost universally adopt the French unit, which is a representation of the amount of force required to raise one gramme through one centimetre of distance in one second.

a very easy matter, in testing the excitability of nerves or in reporting cases treated by electricity, to state exactly how many milliampères passed through the nerve or through the system ; in other words, it would seem easy to have a dosage of electricity comparable to that of medicines. Unfortunately, the affair is not so simple, chiefly on account of the diffusion of the electrical current which naturally takes place during its passage through the human body. If, for instance, an electrode of a square inch of surface be used, the effect upon the organism must be different from that which would be obtained by employing an electrode of twenty square inches. In the one case a concentrated current would pass at least for some little distance into the body, in the other a large number of proportionally feebler currents would enter from the beginning. More than this, when it is intended to galvanize a fixed spot, as a ganglion or nerve-trunk, it is rarely possible to note exactly what portion of the current which enters the body reaches the desired spot and how much of it is diffused through other tissues. (See paragraph on conduction.) In order, therefore, to compare results obtained by different electricians, or by the same electrician upon the same case in successive days, or in different cases, it is essential to know exactly the size of the electrodes and the positions at which they were placed upon the body. To facilitate measurements, Mr. C. W. Müller has proposed that in therapeutic electricity a fraction be used to express the concentration of the current which is employed, the numerator of the fraction to consist of the number of milliampères, the denominator of the number of square centimetres in the electrode. Thus, the fraction $\frac{1}{30}$ would mean that a current of one milliampère strength had been employed with an electrode of thirty centimetres of surface, while the fraction $\frac{4}{16}$ would mean that the current of four milliampères had been employed through an electrode of sixteen square centimetres of surface. These fractions do not express in any way the relative positions of the electrode, and the alteration of half an inch in the position of an electrode on the surface of the body may double or halve the amount of a current which reaches the desired spot. Practical dosage of electricity in therapeutics is probably a chimera, and certainly has not yet been satisfactorily achieved. It is possible that in certain delicate cases, with very careful investigators, the measurement may be employed with advantage for the study of physiological results. But one who is familiar with the average training in physical science of physicians who use electricity must recognize that the publications of electrical measurements amount to little more than a show of scientific accuracy.

For ordinary use in diagnosis and treatment of disease galvanometers are not required, the experienced medical electrician being sufficiently guided by the sensations of the patient and the muscular effects achieved.

A dense fog has been thrown around the subject of electro-therapeutics by the idea that there are various essentially different forms of electricity. The current which flows from a cell or a combination of cells is spoken of as a *continuous current*, or sometimes as a *primary current ;* besides this,

modern therapeutists use another series of currents, which are known as *induced currents*.

The term *primary current* is often applied to one of these induced currents. If we employ the name *continuous current* for that current derived from the galvanic cell, we must continually be speaking of the interrupted continuous current, which certainly is inelegant. We shall, therefore, employ the name *chemical current* or *galvanic current* to designate that form of electricity which is generated in the galvanic cell.

If a coil of insulated wire have a bar of soft iron placed in its centre and be surrounded by an external coil of wire, when a chemical current is passed through the first coil, owing to physical laws which it is not necessary here to consider, every time the galvanic circuit is completed or interrupted a brief current of electricity is induced in the inner or first coil, and also a similar current in the outer or second coil. The only physical facts which it is necessary for us to know are that these induced currents are very brief and of great strength, also that they are to-and-fro currents,—that is, run in opposite directions in each individual coil. Thus, in the inner or first coil, when the galvanic circuit is closed, the induced current in the inner coil runs parallel to the generating chemical current; but when this latter current is broken, the induced current runs in a contrary direction. In the outer coil, the induced current, which is instantaneously developed when the galvanic current is sent through the inner coil, pursues a direction opposite to that of the chemical current; but when the latter is broken, the return induced current in the outer coil runs parallel to the generator current.

As these induced currents run backward and forward, to and fro, in this way, it would appear that there could not be any negative or positive pole to the battery which generates them, for if one end or pole of the wire constituting the coil be negative in regard to the first induced current, it must be positive in regard to the second or return current. This is assuredly true so far as concerns the outer or second coil, but is not true for the inner or first coil, as is readily understood by means of the diagram of an induction battery given on page 48.

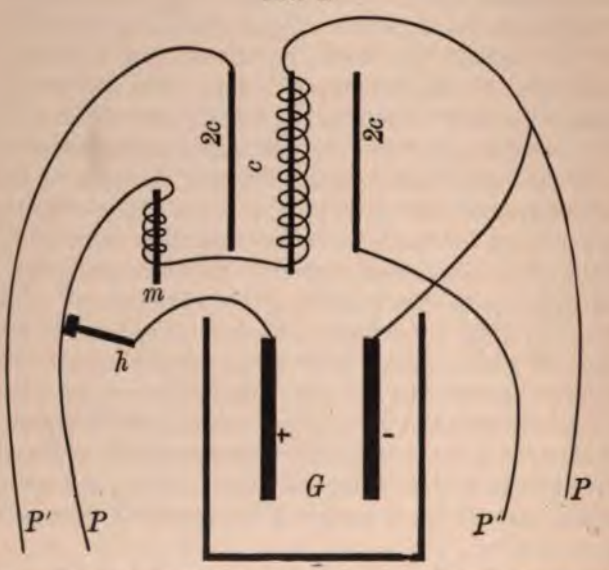
It is plain that when the current is passing, the hammer *h* being in the position represented in the diagram, *m* will become magnetic and attract *h*. This at once breaks the current, and an induced current runs through the first coil and is received by the patient grasping the handles *P P*. The instant the current is interrupted, *m* loses its magnetism and the spring-hammer flies back. Now the circuit is closed, and for the second time an induced current runs through the first coil, *c*. It is evident, however, that this induced current of closure will not pass through the body of the person grasping the handles *P P*, but will pass along *h* through the cell to the other end of the coil, as a shorter route and one of vastly less resistance. It is plain that from the inner or first coil the induced current of broken circuit alone passes through the body of the patient.

In regard to the outer coil, it is evident that when the circuit is closed

the momentary induced current must run through the body of whoever grasps the handles P' and P', and that the return current which passes when the circuit is broken must take the same route.

It follows from the above considerations that the *current of the first coil* runs through the patient in *one direction only*, and electricians may

FIG. 2.



G, galvanic element, with the + and — metals in it; *c*, coil in which the primary induced current, or current of the first coil, is generated; *h*, spring-hammer or vibrator; *m*, a piece of soft iron becoming a magnet when the current is passing; *2c*, outer coil in which the secondary induced current, or current of the second coil, is generated; *P*, handles of inner coil; *P'*, handles of outer coil.

correctly mark poles + and —, but that the *current of the second coil* runs in *both directions*, so that any designation of its handles as positive and negative is incorrect. The only justification for the marking of the secondary or outer current poles, as is often done, is found in the fact that the induced current of the broken circuit is stronger than that of the closed circuit. Hence it is that with very strong currents the two poles can sometimes be distinguished when grasped in the hand. The difference is, however, a slight one, and for all practical purposes the induced current of the outer coil is a to-and-fro one, without any negative or positive poles.

If a strong continuous galvanic current be passed through a person, a shock is felt at the moment of making and breaking the circuit, but while the current is passing no sensation is perceived except at the points of entrance and exit. Or if the current be passed through the nerve of a muscle, that muscle violently contracts at the moment the circuit is made or broken, but while the current is flowing is quiescent. If a rapidly interrupted faradic current be passed through a nerve, the muscle supplied by that nerve is thrown into a continuous spasm. The reason of this is

obvious. The so-called faradic or induced current is, as has already been stated, a succession of instantaneous broken currents for the first coil, and of equally brief to-and-fro currents for the outer coil ; so that the circuit is continually being closed and broken, and the muscle is continually excited to action. There is, therefore, a different result achieved in the application of the continuous and induced currents, not because there is any real difference in their natures, but because the mode of application is diverse.

Many medical electricians teach that the true galvanic current is very different from the faradic current, and many, like Duchenne, persist in asserting that the currents of the first coil are essentially different from those of the second. Galvanism is, however, galvanism, and its nature and attributes are probably always the same. The apparent differences in results are simply due to the variations in the power, the duration, and the direction of the currents. The ordinary faradic currents lack chemical power because they pass so quickly that they have not time to exert a chemical influence. When, however, by proper apparatus the to-and-fro currents of the ordinary faradic machine are separated, and the interruptions made so rapid that the breaks are too short to exert influence, all the chemical and vital effects of the continuous current running in one direction are obtained. It is by virtue of this fact that ordinary street-currents, which are all currents of induction, may be used in human medicine in lieu of the direct galvanic current.

We can readily, by mechanical means and contrivances, interrupt the continuous current, or even rapidly reverse the poles so as to give a to-and-fro current like that of the outer coil. When this is done, it is impossible to distinguish between the action of the galvanic and that of the faradic current in producing muscular contractions. It is true that in certain diseased states of the muscle it has been asserted, and with apparent reason, that the action of the induced current is essentially different from that of the true galvanic current.* But we believe further investigation will show that the seeming differences are really due to the difference in the

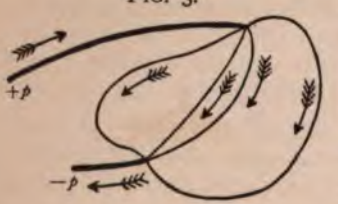
* It is this fact that has led to the belief that there is some intrinsic and inscrutable difference between the induced current and the chemical current. But time is an element required for the propagation of any force. If the hand be passed rapidly through a flame, the latter is not felt ; if the hand move more slowly, a sensation of warmth is perceived ; if the motion be still slower, this sensation becomes pain. Now, if the hand be partially anæsthetic from disease, in order for the sensation of warmth to be perceived motion must be much slower than in the first instance. In other words, more time is required for the partially paralyzed sensory nerve to perceive heat than for the normal nerve to do so. What is true of the sensory nerve is true also of the motor nerve. It does not respond so quickly to stimuli when partially paralyzed as when normal. The muscle first loses its power of responding to those faradic currents which are excessively rapid, then to those which are less so, and finally to all induced currents, because from their very nature these currents, even when slowest, last but a fraction of a second. The chemical current may be continued for any length of time at the will of the operator, who is thus enabled to act upon a muscle whose nerve has become so insensitive that it fails to perceive the flash of faradic galvanism. The probable correctness of this theory is shown by the fact that the rapidly interrupted chemical current is no more able to affect the diseased muscle than is the rapidly interrupted faradic current.

lengths of time during which the currents are passing, and not to any inherent peculiarities of the various currents themselves.

It is of the utmost importance to determine by what route or routes galvanic currents pass through the body when the poles are applied to it, and, since the body as a galvanic conductor is governed by ordinary physical laws, some knowledge of these laws is a necessity to the electro-therapeutist.

If a current be passing along a homogeneous conductor, such as a wire of iron, of copper, or of other metal, and that conductor splits up into a number of branches, the current also divides, as is illustrated in the diagram (Fig. 3). If these branches, being of equal size and length, offer an equal resistance, the current divides equally; but if the size or length, and consequently the resistance, of the branches be unequal, the division of the current is unequal; the law being that the strength of the current in each branch of the conductor is inversely proportional to the resistance of that branch. This law is as applicable to conductors composed of many substances as to those composed of a single substance; but then the resistance in a branch depends upon the specific resistance of the substance of which it is composed, as well as upon its size and length.

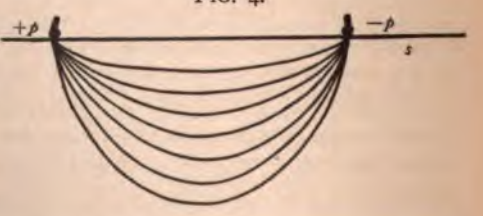
FIG. 3.



In applying these laws to the passage of galvanism through the body, it must be borne in mind that the dry skin offers an enormous resistance to the passage of the current, so that practically none of the latter will pass *along* it. On the other hand, when the skin is thoroughly wet with salt water it allows the current to pass *through* it readily.

Let us suppose, then, that in the diagram (Fig. 4) $+p$ and $-p$ = wetted poles; ss = skin, with the tissues below it. It is evident that, if the tissues were a uniform mass, the current, passing through the skin as a solid bolt, would break up into an infinite number of curved currents, which would meet and pass through the skin again as a solid mass at $-p$. It is equally plain that, of these sub-currents, those whose course was nearest the straight line from $+p$ to $-p$ would be the shortest, and would, therefore, meeting with the least resistance, be the strongest, while as the curve and consequently the length and the resistance increased, the strength of the current would diminish until it became practically null. In this imaginary case the tissue beneath the skin has been supposed to be homogeneous: in actual life the tissue never is homogeneous, and the resistance of the different constituents

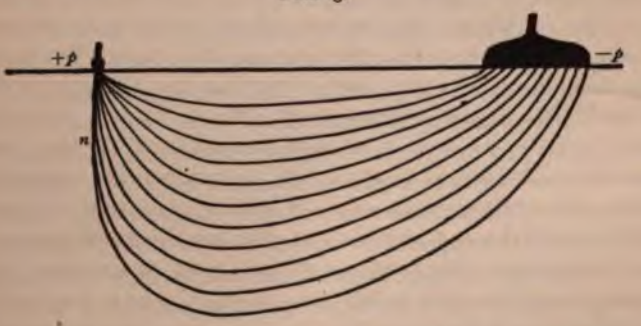
FIG. 4.



varies somewhat. Consequently, the strength of the subdivisions of the current is modified,—those branch streams being increased which run along or through tissues that conduct readily, and *vice versa.*

By remembering these facts, we are enabled to apply electricity as closely as may be to any desired portions of the body. Thus, if it be intended to affect as exclusively as possible a certain spot or minute portion of a nerve, a well-wetted small electrode is placed directly over this portion, and, especially if the nerve be somewhat deeply situated, pressed down firmly, so as to condense the tissues as far as possible into a homogeneous mass, while a large wet electrode is placed at a small distance from it in a situation which the anatomy of the part will readily suggest. The diagram (Fig. 5) will perhaps illustrate this point more clearly than would many words.

FIG. 5.



It is evident that the spot immediately under the small electrode will receive the full strength of the current, which is directly afterwards so broken up as to affect very slightly any other part.

Again, suppose it is desired to pass a current through some length of a nerve ; it is evident, in the first place, that two small electrodes should be chosen, and that they should be well wetted and pressed firmly upon the trunk of the nerve at the two ends of that portion which is to be affected. Again, in applying electric currents to muscles it is found that if the currents be sent through the body of the muscles, only very imperfect and partial contractions occur, unless, indeed, the currents be excessively strong. Duchenne was the first to discover that when one pole is placed over certain spots or points in the muscle, violent general spasms of the muscle are produced by currents usually too feeble to elicit a distinct response. To these places the name of *motor points* has been given. These motor points correspond to the position at which the supplying nerve enters the muscle. When it is desirable to affect chiefly or solely a given motor point, it is evident that one small well-wetted electrode should be pressed firmly over the motor point, and another large sponge electrode placed at some little distance from it, in the manner which has already been explained.

For certain purposes, to be hereafter detailed, it is often desirable to

affect chiefly the skin by the electric current. Under these circumstances the skin should be well dried. It then offers so great a resistance that only currents of considerable strength are able to force their way through, and even these currents, taking advantage of the natural apertures formed by the sweat- and other glands, are broken up into a number of branch currents. The galvanic current reaches the internal structures in a great number of small streams very much reduced in power by the resistance they have overcome. If the second pole of the battery be a large well-wetted disk or sponge at a distant part of the body, it is evident that these branch currents will separate and subdivide in such a way that their effect upon the deeper structures will be almost entirely lost.

Ohm's law does not govern electricity upon points, since the force accumulates on the extreme end of the point until its density is excessive, and its self-repulsive power becomes so great as to overcome all resistance and to break off highly electrified particles of the conductor, which fly off through the air. It is this that renders the so-called "electric brush" so energetic in its action on the skin. This instrument consists of a number of wires united in the form of a cylindrical brush and connected with one pole of the battery ; when this is brought in contact with the skin of a person, on whom at some distance is placed the other large well-wetted electrode, each wire point offers a dense accumulation of electricity, which forces its way at all hazards through a minute portion of the skin. The whole current, of course, enters the deeper tissue in an infinite number of subdivisions, and consequently its effect on these tissues is reduced to a minimum.

THERAPEUTIC APPLICATION.—Most of the therapeutic applications of electricity are considered in this book under special headings, but it seems proper at this place to call attention to the use of the current for the relief of various local *rheumatic* affections. In subacute or chronic muscular rheumatism faradization is often of great service, and even in rheumatic diseases of the joints it sometimes brings marked relief. When the symptoms are acutely inflammatory they must first be subdued by suitable measures ; but when they are subacute the current may be employed at the beginning of the attack. It should be rapidly interrupted and as strong as can be borne by the patient. The first séance should last but five minutes, but the time of application can be gradually protracted to fifteen or twenty minutes.

Motor System.—Galvanic currents are employed in paralytic affections for three distinct purposes,—namely, *diagnosis*, *prognosis*, and *therapeusis*. These we shall consider in the order in which they have been named.

There are certain palsies, such as pseudo-muscular hypertrophy, in which the muscular structure is so destroyed independently of any involvement of the nervous system that no response to the galvanic current is possible. All of these palsies are, however, essentially exceedingly chronic, and their diagnosis is to be made out chiefly by a microscopical examination of the muscles themselves. When a paralysis is due to lesion in the brain or in those portions of the spinal cord which have no trophic

influence, no changes occur in the muscle except the very gradual alterations due to disuse. On the other hand, if, by disease of the trophic cell in the spinal cord, or by disease or injury of a conducting nerve, a muscle is entirely deprived of the influence of the spinal centres it rapidly undergoes structural change. When a muscle is degenerating for want of spinal influence, it first loses its power of responding to rapidly interrupted faradic or chemical currents, then to slowly interrupted faradic currents, then to slowly interrupted chemical currents, and lastly to slowly reversed chemical currents. During this period of degeneration it is possible to elicit with the galvanic current the so-called *reaction of degeneration*, first discovered by Brenner. To demonstrate these reactions it is essential to apply the electrode to the muscle: if the electrode be connected with a nerve-trunk of a degenerating muscle it will be found that reaction is diminished in quantity but not altered in quality. When a feeble galvanic current is used, and the negative pole (cathode) placed over the normal muscle but not over its motor point, a strong contraction occurs at the closure of the circuit; when, however, the positive pole (anode) is placed over the normal muscle, the contraction is much less; in neither case is there any contraction when the circuit is broken: in other words, with the normal muscle and a feeble current we obtain good cathodal closing contraction, slight anodal closing contraction, and no motion whatever at either cathodal opening or anodal opening. When a current of sufficient power is used, opening contractions are produced, and the anodal contraction is greater than the cathodal. The reaction of degeneration consists merely in a more or less perfect reversal of the above formula. The anodal (positive pole) closure then causes a stronger contraction than the cathodal (negative pole) closure. When there is only a slight degree of degeneration present, there is a correspondingly slight increase of anodal closing over cathodal closing contraction. A minimum degeneration would be indicated by an equality of the two closing contractions.

These alterations in the electrical relations of a degenerating muscle may be formulated, and in this way are perhaps more readily grasped by the student. The symbols are as follows: An Cl C represents *anodal closing contraction;* An O C represents *anodal opening contraction;* Ca Cl C represents *cathodal closing contraction;* Ca O C represents *cathodal opening contraction;* $<$ represents *is less than;* $>$ represents *is more than* (the point of the $<$ being towards the lesser quantity). Then the formulas are:

An Cl C $<$ Ca Cl C
An O C $>$ Ca O C } muscle normal.

An Cl C $=$ Ca Cl C
An O C $=$ Ca O C } muscle in the first stage of degeneration.

An Cl C $>$ Ca Cl C
An O C $<$ Ca O C } muscle in a more advanced stage of degeneration.

After the latter reactions of degeneration (De R of some authors) have been established, if the muscle continues to undergo change, the

galvanic irritability slowly diminishes, stronger and stronger currents being required to produce an effect. When a certain stage is reached, all reactions cease, save a feeble An Cl C, and at last this is lost and the muscle does not respond at all. When recovery occurs, the electrical reactions of the muscle pass upward along the pathway they have descended.

The practical importance of the reaction of degeneration is greatly lessened by the circumstance that its demonstration usually requires much skill and patience,* and that it probably is never present when a muscle still retains its integrity as regards the faradic current. For the purposes of the practitioner, the failure of response to the latter current is the best test as to the condition of a muscle. When a muscle loses its power of responding to the rapidly interrupted faradic current in a week or ten days after the occurrence of paralysis, whether the reaction of degeneration can or cannot be satisfactorily demonstrated, the inference is very positive that the lesion either is one of the nerve-trunk or, if of a nerve-centre, is of such a character as seriously to involve the trophic cells of the spinal cord. If a few days later such muscle is unable to respond to any faradic current, this inference becomes a certainty. Under these circumstances, the possible lesion is narrowed down to poliomyelitis, a conceivable destructive myelitis, and an affection of a nerve-trunk.

The persistence of muscular contractility intact for some weeks after the occurrence of a palsy depending upon an organic lesion proves that the disease is of cerebral origin, or, being spinal, is of such nature as not to compromise seriously the trophic nerves of the cord.

In applying these rules, it must not be forgotten that whenever a muscle is not used it loses its contractile power, so that even in paralysis from cerebral hemorrhages the muscles finally degenerate, although this degeneration is rarely so complete as in peripheral palsies. It is not the fact of degeneration, but its degree, and especially the period of time which elapses between its occurrence and the commencement of the paralysis, that is the important factor in the diagnosis. In cerebral palsies no distinct loss of functional activity in the muscles is usually perceived sooner than six weeks after the onset of the attack ; and even after years have elapsed some response may often be elicited by strong slowly interrupted or reversed currents.

There are certain palsies in which the electro-muscular contractility is really or apparently above normal. Very frequently the excessive contractions produced are not so marked in the muscles to which the currents are applied as in other muscles, whose movements are in reality reflex in their nature. In all these cases the probabilities are that there is a condition of acute hyperæmia or of excessive functional irritability of the spinal cord.

In *hysterical paralysis* any aid to diagnosis is often of very great

* In attempting to bring out the reaction, the clock-work current-breaker as usually furnished by instrument-makers is useless; the hand current-breaker may be employed, but almost requires an assistant. Hence some electricians use a pedal rheotome, which enables the operator to cut off the current without moving his hands.

value, and it has been asserted that in this class of palsies the preservation of electro-contractility with loss of electro-sensibility is always present, and is of diagnostic import. Our experience, nevertheless, is very positive that in hysterical palsy both electro-contractility and electro-sensibility are frequently normal. When, however, the paralyzed muscle responds to galvanic currents, and the patient is to a great extent, or altogether, insensible to their passage, a very positive diagnosis of hysteria may be given. The electro-contractility is never seriously compromised in hysterical palsy.

In using galvanism as an aid in *prognosis*, the condition of the muscular contractility is always to be considered in conjunction with the nature of the lesion and the length of time it has existed.

Taking first ordinary *hemiplegia* as the type of *cerebral* palsies, it must be borne in mind that the actual existent amount of paralysis is really the product of two essentially different factors. The nerve-centre is primarily damaged, and after a time the muscle also suffers loss of structural integrity from want of use. The restoration of the nerve-centre does not necessarily involve the restoration of the muscle, so that in a case of hemiplegia of some standing the cerebrum may have recovered itself partially or entirely, and yet the muscle be in such a state of degeneration as to be unable to respond to the impulse transmitted to it from the nerve-centre.

Under these circumstances, galvanic treatment, although unable to affect the nerve-centres to any extent, does great good by restoring the muscular tone. It is manifestly impossible in such a case to determine before treatment how far the nerve-centre has recovered itself, or, in other words, to what extent the existing paralysis is of centric and to what extent of muscular origin. When, in a case of apoplectic hemiplegia, there is no recovery of the power of voluntary movement after the lapse of six weeks, the prospect of decided improvement from electrical treatment is very gloomy, because the probabilities are altogether in favor of the existence of a serious, persistent centric lesion. If, however, there is some motion, the probabilities of improvement are inversely proportionate to the structural health of the muscles,—*i.e.*, the worse the state of the muscle the better the expectation of relief. If the tone and the electro-contractility of the muscles are normal, the centric factor is the chief one in the production of the paralysis, and little good is to be achieved by the use of the galvanic current. On the other hand, if the muscles have undergone a very decided degeneration, much good is to be expected. No hopes of absolute cure should, however, be held out, because, in the great majority of cases, after the muscles have been fully restored the nerve-centre is found to be more or less damaged. The improvement under the use of electricity is usually at first rapid, but after a time ceases altogether, because, the muscles having recovered their tone, it is not possible to affect to any great extent the sole remaining cause of the paralysis,—*i.e.*, the centric lesion. Under these circumstances it is useless to continue treatment.

In *poliomyelitis*, early in the attack the galvanic current is of little value in determining the prognosis, except that the general law is, that the more rapidly electro-contractility is lost the more serious is the case. In advanced cases the duration of the attack and the condition of the electro-contractility in the muscles are both to be considered. If no response to an electric current can be obtained, the prognosis is always very grave ; although even under such circumstances a decided improvement has occurred in a small percentage of the cases we have treated. If the case be an old one, the preservation of some degree of electro-contractility indicates that the structural lesion in the cord is not a fatal one ; and as, under these circumstances, the muscles can always be more or less perfectly restored, the prospect of improvement is very good. The preservation of electro-contractility late in the disorder, when the centric lesion is no longer progressing, is of much more import than it is in the first few weeks or months of the case, when the central trouble may be increasing.

In *peripheral palsies* the prognosis depends upon the nature of the nerve-lesion rather than upon the condition of the muscle ; but it must be remembered that when a muscle has absolutely lost its power of responding to any electrical current its restoration is always a matter of difficulty and of some doubt.

In regard to *therapeusis*, the first point to be determined in acute cases is, very often, when to commence electrical treatment. When the lesion is of such nature as not to provoke any irritation of the nerve-centre, no time should be lost. Thus, if a man is unable to use his arm because he has slept with it under his head and thereby paralyzed the nerve by pressure, galvanism should be at once employed.

When, however, the lesion is of such character as of necessity to irritate the nerve-centres, the case is different. The local stimulation of the peripheral nerve-fibres by the electrical current does, in some way not yet definitely understood, affect the nutrition of the nerve-centres ; and when these nerve-centres are in a state of active excitement or inflammation, a peripheral galvanic irritation may do serious injury. Hence the rule that when an acute palsy is connected with active irritation of the nerve-centres, galvanism should not be used upon the muscles until the centric disturbance has subsided. Thus, in *hemiplegia* from cerebral hemorrhage the muscles must be allowed to rest not only until all symptoms of centric irritation have passed away, but also until the brain has become so accustomed to the clot that the latter no longer acts as a foreign body. It is usually from three to six weeks before electricity can be used with advantage in these cases. Again, in acute *cerebritis*, *cerebral* or *spinal meningitis*, and *myelitis*, the employment of galvanic currents should be strictly forbidden until a stage is reached when the effects of the inflammation, and not the inflammation itself, are to be dealt with.

When it has been decided to commence the use of electricity, it is next to be determined what current shall be employed. It has already been shown that there are no inherent mysterious differences in the various

currents ; yet there is a practical difference, and the clinical rule of choice is, *Always select that current which produces the greatest amount of muscular contraction with the least amount of pain ;* trying the rapidly interrupted faradic or the rapidly interrupted chemical current and the slowly interrupted faradic or the slowly interrupted chemical current, and always, when these fail to elicit response, the slowly reversed chemical current, which, if necessary, may be increased in strength until the patient can no longer bear the pain.

The current having been selected, the *individual muscles* must be galvanized at each séance.

After what has been said, it is not necessary to speak at this point as to the best methods of applying the currents to the muscles, but only to insist upon the fact that it is not so much the electricity as the contractions induced by it that benefit the palsied parts, and that consequently the electro-motor points of the muscles should always be separately reached. The diagrams given in the Appendix will point out more clearly than would any description the approximate positions of the motor points, which vary somewhat in their location in various individuals. Some deep-seated muscles we are not able to reach directly, but we can reach them indirectly by galvanizing the nerves which supply them.

There are certain precautionary rules which must never be lost sight of in the electrical treatment of palsies. Pain is an evil, and its infliction is always to be avoided as far as possible. Hence the rule never to use stronger currents than is necessary. It is very possible to fatigue a healthy muscle, much more a diseased one. A weak muscle may be greatly injured by being over-fatigued. Hence the rule that currents are not to be applied to muscles sufficiently long at a time to induce fatigue. In general, an electrical séance should last from ten to twenty minutes, no one muscle being subjected to the currents for more than five minutes, and it may be repeated daily, or three times a week.

Sensory System.—Affections of the sensory nerves are of three kinds, —pain, hyperæsthesia, and anæsthesia. The use of electricity for the relief of these disorders is almost entirely empirical,—indeed, is often purely experimental in an individual case, as no clinical laws regulating the use or enabling us to decide as to the applicability of the agency have as yet been worked out.

It may be laid down, however, as an axiom, that the galvanic current is powerless to relieve the *pain* of phlegmonous *inflammations*, and that its use should be restricted chiefly to nervous pain or neuralgia. It is also true that the currents are possessed of no therapeutic power over neuralgia dependent upon central organic lesions ; this is also probably true of such neuralgias as *migraine*, *malarial hemicrania*, and some *toxic neuralgias*, in which, although there is no perceptible organic lesion, there is some deep-seated, inherent deficiency either in the central nervous system or in the constitution or condition of the patient.

When, as in *sciatica*, the so-called neuralgia is due to a neuritis,

galvanism may be of great service. It should not be applied, however, until the stage of very acute inflammation is past. In regard to the selection of the current, our experience is that it must be purely empirical. The most usually successful is a very mild (four to eight cells) chemical current, which should be passed steadily for ten minutes down the nerves. It should not be so strong as to give actual pain, and must not be interrupted. As in the great majority of cases this method of application yields the best results, it should always be tried first. When it does good, it *nearly always* affords relief during the passage of the current, at once or after, at the most, two or three sittings. Further, the period of relief soon begins to extend beyond the séance and gradually grows longer and longer. Some cases receive most benefit from a rapidly interrupted faradic current, which should therefore be tried if the continuous current fails. To the employment of electricity should, of course, always be added the proper local and constitutional treatment of the case.

In *hysteria*, in some cases whose nature is very obscure, and rarely as a sequela or result of a serious cerebral or spinal lesion which may have been more or less completely recovered from, there exist *local anæsthesias* of the skin. When these are not dependent upon a too serious organic lesion, they are often very much benefited, or even cured, by the use of the electric brush. This should be large and composed of fine wires, while the other electrode should consist of a large, well-wetted sponge, placed upon a distant part of the body. Either the faradic or the chemical current may be employed ; in either case it should be a very strong one. Toxæmic anæsthesias, such as those sometimes produced by arsenic, we have seen benefited by electrical treatment with the dry brush.

Application to the Nerve-Centres, and Use as a Tonic.— Galvanism in various forms has been applied locally to the nerve-centres in various diseases. In regard to the brain, we have never yet met with any clear clinical evidence of good having been accomplished ; and, with our present physiological knowledge, it is difficult to imagine in what way or under what circumstances cerebral galvanization can produce good results. On the other hand, harm certainly has been wrought by the application of strong currents to the head. Galvanic currents passed through the brain can act only as irritants, and we agree entirely with the dictum of Cyon (*Principes d' Electrothérapie*, Paris, 1873), that galvanization of the head ought to be abandoned.

An enormous amount of influence in all sorts of diseases has been claimed for the so-called *galvanization of the cervical sympathetic.* The situation, however, of the upper ganglion deep beneath the carotid artery makes it extremely improbable that it can be reached by any suitable galvanic current from the outside ; and the fact is that it is impossible by means of therapeutic currents to produce any stimulation of the ganglion sufficient to call forth the slightest manifestation of functional activity. What is true of the galvanization of the sympathetic nerve is equally true of the galvanization of the spinal cord. It is not possible

by therapeutic currents to affect either of these nerve-centres from the exterior of the body.*

The faradic current is without doubt, when properly applied, capable of acting as a general stimulant to the circulation and to the nutrition of the muscles, and it has been shown by S. Weir Mitchell that general faradization may temporarily elevate the general bodily temperature. In these cases the current produces wide-spread muscular contractions, and it is doubtful how far these are the cause of the quickening of the circulation and how far the arterioles are directly affected by the electricity ; it may also be that nutritive cell movements through the body are quickened by the current.

Various methods have been published by authorities for using electricity as a general stimulant, but the experience of many years has led us to employ exclusively the faradic current ; applying it first with slow interruptions to the various muscles and groups of muscles throughout the body in regular succession. The operator should begin with one leg or one arm, place the electrodes on the motor points, and proceed systematically.

In order to get the best results, the séance should last from forty minutes to an hour, and should be divided into two parts. Thirty to forty minutes should be occupied in the first part, during which the effort is to bring into contraction almost every muscle in the body. The current used should be a slowly interrupted one, of such strength as to produce powerful contractions. Beginning at one or other of the extremities, and bearing constantly in mind the position of the motor points, the operator should go over the whole body, not forgetting the muscles of the chest, back, and abdomen. After the muscles of the body have been gone over a large electrode should be placed at the nape of the neck or high up between the shoulders, and a second in such position that it will come in equal contact with the two feet, and for twenty minutes a very rapidly interrupted current, as strong as the patient can bear without suffering, should be passed through the body. It is entirely possible that such current acts by stimulating to contraction the muscle-fibres in the walls of many of the small blood-vessels.

MAGNETISM.

Various clinicians assert that they have obtained extraordinary therapeutic results from the use of magnets, but in an elaborate investigation made by F. Peterson and A. E. Kennelly with magnets of enormous power upon frogs, dogs, and human beings it was conclusively shown that magnetism has no demonstrable effect upon the animal ; and it must be concluded that the therapeutic effect of magnets is confined to their psychical influence (*New York Med. Journ.*, 1892, vol. lvi.).

* A detailed discussion of the evidence upon this matter may be found in the tenth edition of this book. It has been omitted here as unnecessary, and as having long stood practically unanswered.

PART II.

DRUGS:

A SKETCH OF THEIR NATURAL HISTORY AND PHARMACEUTICAL PREPARATIONS, WITH AN EXHAUSTIVE STUDY OF THEIR PHYSIOLOGICAL, THERAPEUTICAL, AND TOXICOLOGICAL ACTIONS.

PRELIMINARY CONSIDERATIONS.

ALTHOUGH PHARMACY, or the science of preparing medicines, is entirely distinct from THERAPEUTICS, or the science of the application of medicines to the cure of disease, it is evident that some acquaintance with the former is necessary to the correct appreciation of the latter. Further, the basis of each of these studies is a knowledge of MATERIA MEDICA, or the substances used as medicines. PHARMACOLOGY is the general term employed to embrace these three divisions.

In every civilized country there is some recognized official list of drugs and their preparations, known as the *Pharmacopœia*. In most places, this, being prepared with the sanction of the government, partakes of the nature of a law, but in the United States conformity to it depends upon the voluntary action of the professions of Medicine and Pharmacy, by a representative convention of which it was originally prepared and is decennially revised.

The preparations made from crude drugs are as follows :

DECOCTA.—*Decoctions* are made by boiling crude drugs for a greater or less time in water. It is evident that this method of preparing is ineligible when the active principle is volatile or is easily decomposed by heat, or when the drug contains much starch, whose extraction would make the preparation very thick and predispose it to rapid decomposition. The method is especially adapted to hard, woody substances, and to those containing much albumin, which is coagulated by the boiling water and left in the original drug.

INFUSA.—*Infusions* are made with water, either cold or hot, without boiling. They are prepared by maceration or by displacement.

LIQUORES.—*Solutions* are preparations in which an active, *non-volatile* principle is dissolved in water.

AQUÆ.— *Waters* are solutions of *volatile* principles in water.

MISTURÆ.—*Mixtures* are preparations in which one or more medicinal substances are held in suspension in water. Of such nature are emulsions, in which some oily material is suspended by a gummy or an albuminous body.

MUCILAGINES.—*Mucilages* are solutions of gummy substances in water.

SYRUPI.—*Syrups* are sugary liquids, the menstruum or basis of which is water, with, in some cases, vinegar or alcohol.

MELLITA.—*Honeys* are preparations whose basis is honey.

ACETA.— *Vinegars* are preparations in which vinegar or dilute acetic acid is used as the menstruum.

TINCTURÆ.— *Tinctures* are alcoholic solutions prepared by maceration or displacement from the crude drug, or by dissolving *non-volatile* principles. In some of them strong, in others dilute, alcohol is used.

SPIRITUS.—*Spirits* are alcoholic solutions of volatile principles, made by direct solution or by distillation from the crude drugs.

VINA.— *Wines* are preparations whose menstruum is wine.

GLYCERITA.—*Glycerites* are preparations in which glycerin is the solvent.

OLEA DESTILLATA.— *Volatile, distilled,* or *ethereal oils* are active principles obtained from plants by distillation or by other processes. They have no chemical relations with fixed oils, and are readily to be distinguished by the fact that the stain which they leave upon paper disappears in a little time. They are usually composed either of carbon and hydrogen, or of carbon, hydrogen, and oxygen, to which, in the case of certain bad-smelling oils, sulphur is added. By oxidation they are converted into resinous compounds. They are all inflammable, usually of powerful odor, commonly, but not in all instances, lighter than water, slightly soluble in water, and freely soluble in petroleum benzin. By the destructive distillation of various organic substances are obtained products resembling somewhat volatile oils. These are the so-called *empyreumatic oils.*

OLEATA.—*Oleates* are solutions of definite principles in oleic acid.

OLEORESINÆ.—*Oleoresins* are concentrated preparations composed generally of a volatile oil and a resin. They are really ethereal extracts, made by the action of ether upon the crude drugs ; in the case of ginger, a mixture of alcohol and ether is used.

SUCCI.—*Fresh juices* are obtained by expression of the green plant, enough alcohol being added to preserve them.

EXTRACTA.—*Solid extracts* are of two kinds ; one being prepared by the evaporation of the fresh juice, the other being made in various ways from the crude drug.

EXTRACTA FLUIDA.—*Fluid extracts* are very concentrated fluid preparations, generally so made that one minim represents one grain of the crude drug.

RESINÆ.—*Resins* are peculiar solid vegetable active principles, soluble in alcohol and insoluble in water, most of which are obtained by the precipitation of saturated tinctures with water. The majority of the official resins are purgatives.

CONFECTIONES.—*Confections* are medicinal substances beaten up with sugar into a pasty mass.

TROCHISCI.—*Troches*, or *lozenges*, are gummy pellets or disks, so made as to dissolve slowly in the mouth.

SUPPOSITORIA.—*Suppositories* are conical bodies, prepared for introduction into the rectum, where they melt with the heat of the body. Their basis is generally cacao butter.

UNGUENTA and CERATA.—*Ointments* and *Cerates* are fatty solid preparations for external use. The cerates containing wax (*cera*) are the firmer of the two.

EMPLASTRA.—*Plasters* are solid substances spread by the aid of heat upon muslin, skin, or other similar material, and of such nature as to be adhesive at the temperature of the body.

CHARTÆ.—*Papers* are medicated leaves or sheets of paper for external use. The only official papers are those of mustard, of potassium nitrate, and of cantharides.

LINIMENTA.—*Liniments* are liquid preparations, generally soapy or oily, and always intended to be applied externally by rubbing.

The names PILULÆ (*Pills*) and PULVERES (*Powders*) sufficiently indicate the character of the preparations.

The effects of medicine are commonly divided into the *primary* and the *secondary*, or the *immediate* and the *remote*. An example will probably show the difference between these in the briefest and most forcible manner. Thus, the immediate effect of a diuretic is increased urination ; the secondary effect may be removal of serous effusion in some part of the body. It is evident that the latter is brought about not by the medicine itself, but by the changes it induces ; the increased excretion causing a diminution of the amount of the fluid in the blood-vessels, which in turn leads to absorption.

The term or expression *indication* for a given remedy, being in constant use, ought to be distinctly understood ; by it is meant the pointings of nature, or, in other words, the evident needs of the system. Thus, hard fæces collected in the colon are an indication for a purgative of such character as will produce watery secretions to soften them. Relaxation in a part indicates a remedy that will awaken into new life the natural contractility of the part,—*i.e.*, an astringent. Again, the suppression of secretion from over-excitement, or from irritation, is an indication for some drug which will allay irritation ; while the same suppression, when dependent upon torpor or loss of cell-activity, will call for an excitant,—an irri-

tant. The childish absurdity of treating symptoms by any such law as "similia similibus curantur" or "dissimilia dissimilibus curantur" is at once apparent. The same symptoms may be the result of absolutely antagonistic conditions and require absolutely opposite treatment. Without occupying space with details, one example will suffice. Either irritation or depression of the stomach may cause vomiting. Therefore in one case of vomiting a stomachic stimulant such as ipecacuanha, which when given freely in health will produce vomiting, may relieve the nausea because the depressed stomach needs a stimulation to bring it to the normal level; in another case a stomach which rejects food because it is irritated needs a sedative like bismuth, which in health will not produce vomiting. In the first case the law of similars seems to hold good, in the second the law of dissimilars appears to be dominant. A law of nature has no exceptions. If an alleged law of nature has exceptions it is not a law. If it were proved that under certain circumstances the earth without the intervention of any second force repels bodies, we should know that the alleged law of gravity is not a law. It is plain, therefore, that neither of the alleged therapeutic laws of similars or of dissimilars is, in truth, a law. They are the results of coincidence, the expressions of half truths. Symptoms are, indeed, but the surface-play of disease, and the rational therapeutist always seeks their hidden meaning. The conscientious physician refuses to practise upon homœopathic, allopathic, or any other restricted basis, but gleans therapeutic knowledge from all sources, guiding himself as far as may be by the light of reason and science, but hesitating not to go beyond into the region of the unknown and uncertain when distinctly led by the lantern of empiricism.

By far the greater number of remedies are absorbed into the blood, and thus find access to the part upon which they act. It is necessary, therefore, for them to be so placed that they can be taken into the blood-vessels.

There are five paths of entrance for medicines into the circulation,—the stomach, the cellular tissue, the rectum, the skin, and the lungs. By far the most frequently employed of these is the *stomach*. It is evident that, in order to pass rapidly and readily into the absorbents, medicines must be in solution. When administered by the stomach, however, it is equally plain that solubility in an ordinary menstruum, such as water, is not a *sine quâ non*, since the varying acidities, alkalinities, and organic contents of the alimentary juices give to them a solvent power far above that of less complex and varying fluids. Thus, a medicine insoluble in water may be dissolved by the acids of the gastric juice, while another drug may owe its activity to its solution by the alkalies or by the fatty matters of the intestinal fluids.

The dissolving power of the *rectal fluids* is very slight: hence, in order to act efficiently, medicines when given by the rectum must be in solution or be readily soluble. Absorption, moreover, does not occur so rapidly from the rectum as from the upper bowel, and a longer time is therefore

needed to impress the system in this way. In the great majority of cases medicines are thus exhibited to obtain peculiar effects more or less local in character. Thus, an opium suppository is given in dysentery, or to quiet irritation of the genito-urinary organs.

Medicines which are thrown into the *subcutaneous tissue* are said to be administered hypodermically. The syringe employed is provided with a sharp needle, which must be kept scrupulously clean and free from rust. The medicine must be in perfect solution and not too irritating. The advantages of this method of exhibition are promptness and certainty of action. If twenty minutes be required for the absorption of a certain medicine from the stomach, forty minutes will be usually necessary when it is exhibited by the rectum, and five minutes when it is thrown into the subcutaneous tissue. The objections to the hypodermic method are, first, the danger of producing local inflammation and abscesses ; second, the possibility of throwing the whole mass directly into a vein and having it swept in concentrated form into the heart or nerve-centres. We have seen the injection of a sixth of a grain of morphine followed inside of a minute by complete unconsciousness, collapse, arrest of respiration, dropping of the jaw, and apparent death. The danger of such a mischance can be greatly lessened by withdrawing the point of the needle an eighth of an inch, after it has been plunged into the tissue. The local irritation occasioned by hypodermic injections has not only very frequently produced abscesses, but in not a few cases has caused fatal tetanus. Excessive irritation can be largely prevented by certain precautions, but there are many medicinal substances whose hypodermic employment might be advantageous were they not too irritant for such use. In all cases solution must be complete, and if the medicinal substance be of such nature that it is liable to be precipitated by alkalies, an excess of acid should be present in the water to prevent precipitation by the juices of the cellular tissue. An irritant which is rapidly taken up from the part may produce at first smarting and pain without creating any permanent irritation, but a small solid particle lying in the cellular tissue is almost sure to cause inflammation and abscess. All hypodermic injections should, therefore, be filtered before being used. It is of the utmost importance, even when a non-irritating substance is employed, that the injection should be absolutely aseptic. No solution which has undergone any decomposition or contains any growth should be used. Ordinarily the solution should be freshly made with boiled water. When hypodermic solutions are intended to be kept, they should contain five per cent. of carbolic acid with a drop or two of glycerin to every fifteen minims, which is the maximum amount that should be injected at one time. A considerable proportion of glycerin will throw out of solution most of the alkaloids, but when solution of the medicinal substance is distinctly favored by glycerin, as is the case with extracts, three or four drops of the glycerin should be added to the hypodermic solution. If the injection be thrown directly under the skin, it may, by raising and tearing the skin from its attach-

ment, so interfere with the supply of blood as to cause local irritation. The liquid should, therefore, always be thrown deeply into the tissues, where it may diffuse itself.

There are several ways in which medicinal principles are introduced through the skin, although the only one in common use is the application of medicated fatty preparations, either with or without friction. Absorption takes place, of course, most rapidly at those places where the skin is thinnest,—the inside of the thighs, the surface of the abdomen, and especially the armpits. Absorption will take place through the skin from baths so slowly that medicated baths are rarely used, except for their local influence on the skin. Formerly, medicines were sometimes exhibited by placing them on blistered surfaces, beneath the raised cuticle; at present this *endermic* method is very rarely employed.

In order for a medicine to be absorbed through the lungs in sufficient quantity to affect the general system it must be in the form of vapor or gas.

For *local* purposes medicines are applied to various parts,—to the skin, ear, nares, fauces, stomach, larynx, lungs, rectum, vagina, urethra, etc. For the last three, liquid preparations known as *injections*, or solid ones known as *suppositories*, or, in case of the urethra, as *bougies*, or sometimes as *urethral suppositories*, are employed.

For the purpose of making local applications to the respiratory organs, *atomization* is very commonly practised. Many forms of apparatus are in use, but the principle in all of them is the same. A rapid current of air, or of steam, is forcibly ejected from a horizontal pipe, through a capillary orifice, directly across a similar opening in a vertical tube. The rush of the vapor over this second orifice forms a vacuum; the fluid into which the base of the vertical tube is set, rushing up to fill this, is sucked or drawn out through the orifice, and as it emerges is broken into a fine spray, and is carried along by the current of air or steam into a mouth-piece, at which sits the patient. It cannot be gainsaid that in this way we are able to carry medicinal substances not merely into the larynx, but into the lungs themselves. Volatile medicines vaporized by heat are also sometimes employed in the treatment of lung affections.

There are various classes of agencies which so modify the action of drugs as to necessitate their consideration. Such are disease, climate, habit, temperament, idiosyncrasies, sex, age, time of administration, and emotions.

Disease often fortifies the system against the action of remedies, so that the dose has to be greatly increased to obtain perceptible effects. Thus, pain or delirium tremens will interfere greatly with the production of narcotism by opium. Disease may altogether prevent the action of a remedy. In all these cases two rules should never be lost sight of: first, never give the medicine in such doses as would in health cause death; second, always be sure, before giving large amounts, that the remedy will not make matters worse (as a drastic in intussusception).

Climate, by producing physical habits or tendencies in the patient,

often greatly influences the proper selection and dose of remedies. It is only necessary to allude to the great consumption of quinine in malarial regions as an example.

Habit—including mode of life—seems to alter, as it were, the very constitution of man. Not only does it give type to disease, by producing habitual plethora, or its opposite, but it also fortifies against the action of single remedies, or whole classes of them. Thus, in the opium-eater, a dose sufficiently large to kill an ordinary man serves only to gratify the cravings of appetite. Again, a man accustomed to one narcotic, as alcohol or opium, loses, to a greater or less degree, his susceptibility to all narcotic influence ; and the patient whose bowels require daily to be moved by a cathartic finds that he reacts more and more slowly to medicines of that class. Again, a nervous system blunted by exposure and toil in the open air is far less susceptible to the action of remedies, and requires larger doses to influence it, than does the delicate organization of a woman weakened by indolence and luxury.

Temperaments are peculiarities of organization characterizing classes of individuals ; *idiosyncrasies*, peculiarities belonging to single individuals. This is scarcely the place to discuss the subject of temperaments, but it is allowable to state that while the *phlegmatic* person is no more easily moved by medicinal than by other agencies, the *nervous* individual answers as quickly to the one as to the other. Idiosyncrasies seem at present to be beyond law. They are often very remarkable, and a knowledge of them is most important for the practitioner. Thus, a relative of the authors' is thrown into the most alarming fainting-fits by eating even so much butter as would be ordinarily used as a dressing for vegetables at dinner. Some persons are poisoned by the slightest touch of turpentine, others are frightfully salivated by a mere particle of a mercurial. These idiosyncrasies are numerous, cannot be foreseen, and are often very important : hence the necessity, in prescribing for an unfamiliar patient, of always asking as to his or her peculiarities.

Sex modifies all diseases connected with the organs or the process of generation, but it also does more. Woman is more impressible, less robust, with less power of resisting external agencies, than is man. Consequently, the dose for her should, as a rule, be less than that for him. It is needless to remark here at length on the necessity for abstinence from strongly perturbing remedies during pregnancy or at menstrual periods.

Age, of course, modifies materially the dose. The rule of Young, the one which is the most practical and generally useful, is to add twelve to the age and divide the age by the result. Thus, a child one year old would require one-thirteenth, one three years old three-fifteenths, of the amount necessary for an adult.*

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* Clarke's rule (*Boston Med. and Surg. Journ.*, 1872) is too cumbersome for ordinary purposes. It is based upon relative weights.

"Assuming the average weight of an adult to be one hundred and fifty pounds, for whom an appropriate dose is 1, or one drachm, the dose of most medicines must be in-

Purgatives should usually be given to children in larger, narcotics in much smaller, doses than are called for by Young's rule.

Time of Administration.—Absorption takes place most rapidly in an empty stomach, and consequently, when rapidity of action is desired, the medicine should be given under such circumstances. Thus, a purgative acts soonest when given before breakfast. Substances which are irritating to the stomach should always be administered not only properly diluted, but also when the viscus is filled by a mass of food, which may serve still further to lessen their concentration. Hence such remedies as iodine and arsenic are preferably exhibited after meals. On the other hand, whenever a remedy is especially intended to act on the mucous membrane of the stomach, it should be given when the viscus is empty. Again, some drugs, such as iron, are best dissolved by the acid gastric juice, and it is a matter of some importance to place them in the stomach after eating, when the process of digestion is most vigorous.

Mental Emotion.—Space is wanting to discuss at any length the influence of the imagination upon the action of remedies, and the reader is referred to the delightful book of Tuke for illustrations. Suffice it to state that a positive announcement that a remedy will have a certain effect has often a most remarkable influence in producing that effect, especially on persons of nervous organization and of not too great culture to have faith. We have given a hypodermic injection of a grain of morphine to a man, inducing a degree of hypnotism, and the next day, doubling the size of the injection but withdrawing all morphine, have caused a much more intense effect.

On the Art of Prescribing Medicines.—In the practical use of remedies, very much depends upon the methods of their combination, and, so far as concerns the reputation of the physician, no little importance is to be attached to the mere prescription-writing. The recipes of the master are very widely seen, and he who is incorrect in the grammar or spelling of his English or Latin, or departs without reason from the traditional forms, lays himself open to ridicule, than which nothing is more damaging. A crooked, bad chirography is the traditional mark of literary fame; but absolute plainness should be a *sine quâ non* in the writer of prescriptions. This should also apply to abbreviations: these should be of such a character as not only to be readily made out, but also to be so evident as to afford no shelter to the apothecary whose carelessness has led to serious error. In the case of alkaloids and other powerful remedies, the chief name at least should be written in full. In writing

creased or diminished in the proportion of the weight of the patient to that number of pounds. This proportion is represented by a fraction whose numerator is the patient's weight and whose denominator is 150. If a child at birth weighs six pounds, the appropriate dose for it would be $\frac{6}{150}$, or $\frac{1}{25}$; if it weighs ten pounds, $\frac{10}{150}$, or $\frac{1}{15}$. A child two years old, weighing twenty pounds, would require $\frac{20}{150}$, or about $\frac{1}{7}$ of an adult dose; or, more precisely, $\frac{1}{7\frac{1}{2}}$. A person whose weight is two hundred pounds should have $\frac{200}{150}$, or $1\frac{1}{3}$ of an average adult dose."

the prescription, all the ingredients should first be put down, then the number of doses should be decided upon, and the individual amounts of each substance marked *seriatim*. It is a very good custom always to place first upon the list the strongest of the drugs employed.

The art of combining remedies is not a difficult one ; but in practice certain principles should not be lost sight of. Chief of these are, to prescribe as few remedies as possible, and to use no powerful drug without a very distinct idea of what it is intended to do. Whenever it is desired to give a powerful remedy in increasing doses until its physiological effect is produced, it should always be given by itself. Thus, it may be necessary to give arsenic so as to impress the system, at the same time that iron is indicated ; but the two remedies should be given separately, so that the dose of either can be increased or diminished independently of the other.

The principles of combination, formulated below, were long ago enunciated by Paris, but are to-day as imperative as ever. Medicines are combined,—

First. To augment, correct, or modify the action of a medicine. Thus, purgatives act much more kindly when a number of them are united together. The chief reason of this probably is, that as different remedies affect different portions of the gut, the whole intestine is best reached by a union of the diverse substances. It may take an intense irritation of the mucous membrane to purge as actively as does a mild irritation of both the mucous membrane and the muscular coat.

There are powerful medicines which act similarly upon some parts of the organism, but dissimilarly upon other parts. By combining such remedies powerful effects can be obtained at the points where the two lines of action cross each other, without influencing to a great extent other portions of the system. Thus, chloral produces sleep by its action upon the brain, and also has a distinct influence upon the heart, but none upon the intestinal tract. Morphine acts upon the brain, and does not influence the heart, but has a powerful effect upon the intestinal tract. By combining chloral and morphine we get an overwhelming conjoined influence upon the brain in producing sleep with the least possible disturbance of the heart and of the intestinal tract.

Secondly. To obtain the joint action of two or more diverse remedies. Thus, in a cough mixture, morphine may be included to quiet the cough, while ipecacuanha and squill (in accordance with the first principle) are added to affect the mucous membrane. The application of this principle requires caution, or the practitioner will be led into that chief abomination, polypharmacy. It is worse than futile to attempt to prescribe for every symptom. It is the underlying cause of the disorder or the understratum of bodily condition which must be sought out and prescribed for simply.

Thirdly. To obtain a special combination which is really a new remedy, or which experience has shown acts almost as a new remedy. Thus, when to potassium iodide in solution corrosive sublimate is added,

a new chemical compound is formed, which experience has shown to be of great value in syphilitic diseases. Griffith's antihectic mixture is another instance of the use of chemical changes, the protocarbonate of iron being formed out of the sulphate of the metal and the carbonate of potassium. In the famous Dover's powder no chemical change occurs, but the ordinary action of opium upon the skin is so enhanced that the combination may be looked upon almost as a new remedy.

Fourthly. To afford a suitable form. Thus, acacia is added to make an emulsion, or confection of rose to make a pill. In the choice of excipients, care should be exercised to select a substance free from medical properties, having no chemical incompatibility with the medicinal agent, and of suitable physical character. Bread-crumbs often make a good basis for pills ; but with silver nitrate they are chemically incompatible, on account of the chlorides in them. When writing a prescription, the utmost care should be taken to use such excipients that the combination shall not only be attractive to the eye, but also as little repulsive to the palate as may be. Whenever possible, the pill form should be employed with bitter or disagreeable medicines. The pill may be readily coated with silver-foil ; tonic pills may be coated with iron by shaking or rolling them in ferri pulvis while soft and sticky. Sugar-coated pills and "compressed pills" are liable to get so hard and insoluble that their use requires caution. In regard to mixtures, flavoring oils should be freely used, and the power of glycerin to conceal the disagreeable taste of many substances should be remembered. Whenever practicable, nauseous medicines should be given in capsules. These occur in two forms. *Hard* capsules are prepared to be filled extemporaneously. They can be made large enough to hold ten minims, although this size cannot be easily swallowed by every person without a little training. The soft, flexible capsules are filled by the manufacturing chemists. They can be readily swallowed by most persons up to the size of one drachm. Not only may solid preparations be given in capsules, but also essential oils, volatile liquids, fixed oils, and fluid extracts ; indeed, almost any liquid the dose of which is not too large.

Incompatibilities.—In combining remedies, the subject of incompatibilities must never be lost sight of. The kinds of incompatibilities are two in number,—physiological and chemical. The first of these it would require large space to discuss fully, and any one familiar with the text of the book, if possessed of the slightest reasoning powers, can readily make all necessary deductions.

In many works on materia medica long lists of chemical incompatibilities are given in the accounts of individual drugs. These lists have seemed to us useless, as we have never met with a student who could commit and retain them. Moreover, they contain so much matter of no practical use that the valuable portion is hidden from sight. A certain amount of chemical knowledge is essential to the student, and is not to be taught in a book like the present. He who would ignorantly combine

sulphuric acid and a carbonate needs to restudy his chemical text-book. All that we shall do here is to point out certain principles and a few especial reactions. The following rules may serve for a guide :

Soluble salts which can by mutual decomposition form an insoluble compound will undergo such decomposition when they meet in solution, and will precipitate, unless in some very rare instances, in which a double salt is formed.

Soluble salts which are not capable of forming an insoluble salt never precipitate, and rarely undergo decomposition, when they meet in solution.

Mineral acids decompose salts of the weaker (carbonic, acetic, etc.) acids, and form ethers with alcohol and alcoholic preparations.

Alkalies precipitate the alkaloids and the soluble non-alkaline metallic salts.

Glucosides, such as santonin and colocynthin, should not be prescribed with free acids or emulsin.

Tannic acid and all substances containing it are incompatible with alkaloids and drugs containing them, with albumin and gelatin, and with most soluble metallic salts used in medicine.

Iodine and *iodides* are incompatible with the alkaloids and the substances containing them, as well as with most soluble metallic salts. The *potassium iodide* * should always be prescribed alone, or only in combination with corrosive sublimate (with which it forms a double salt), or with iodine itself.

Tinctures and other *alcoholic preparations* containing resin precipitate the latter when water is added.

Silver nitrate should always be prescribed alone, or in combination with opium or extract of hyoscyamus only. Most vegetable extracts decompose it, and with creosote it is said to make an explosive compound.

Corrosive sublimate is incompatible with almost everything, and should be given in simple syrup : even the compound syrup of sarsaparilla is said to decompose it.

Syrup of squill, containing acetic acid, is incompatible with ammonium carbonate, but not with the chloride.

Lead acetate and *subacetate* are incompatible with almost everything, but are nevertheless frequently used in lotion with opium, the insoluble compound formed being therapeutically active.

Vegetable infusions are generally incompatible with metallic salts.

CLASSIFICATION.—This book has been arranged in accordance with the scheme directly hereafter set forth. Some of the families as here defined are not thoroughly natural, but most of the groups have much of unity in themselves and of propriety in their relations. Thus, antispas-

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* Death has resulted from a prescription containing strychnine and potassium iodide, all the alkaloid being taken at the last dose.

modics are little better than a heap of incongruities, but delirifacients are singularly united together and opposed to somnifacients, while antiperiodics, perhaps, ought to be merged in the alteratives, with which through arsenic they are closely related.

DIVISION I.—SYSTEMIC REMEDIES, substances which act on the solid or fluid tissues of the body.

DIVISION II.—EXTRANEOUS REMEDIES, substances which are employed to act on secretions, excretions, or other liquid or solid bodies which are not human tissues.

SYSTEMIC REMEDIES.

CLASS I.—GENERAL REMEDIES, drugs which affect the tissues of the body generally or such organized systems as reach all portions of the body.

ORDER I.—*Nervines*, drugs which affect the nervous system.

ORDER II.—*Cardiants*, drugs which affect the circulation.

ORDER III.—*Nutriants*, drugs which affect the nutritive movements of the body.

NERVINES.

A. Medicines which act on the cerebrum.

B. Medicines which act on the lower or neuro-muscular apparatus.

A.

FAMILY I.—*Antispasmodics*, feeble cerebral stimulants which are employed for the relief of minor spasms and other nervous symptoms, the result of insufficient nerve-power.

FAMILY II.—*Anæsthetics*, drugs which are used for the production of anæsthesia.

FAMILY III.—*Somnifacients*, drugs which when in sufficient doses produce deep sleep without delirium.

FAMILY IV.—*Delirifacients*, drugs which when in sufficient doses produce delirium, followed by stupor.

B.

FAMILY V.—*Excito-motors*, drugs which produce violent tetanic spasms.

FAMILY VI.—*Depresso-motors*, drugs which cause paralysis.

CARDIANTS.

FAMILY I.—*Cardiac Stimulants*, drugs which increase the arterial pressure.

FAMILY II.—*Cardiac Depressants*, drugs which lower the arterial pressure.

NUTRIANTS.

FAMILY I.—*Astringents*, drugs which call into exercise the vital function of contractility.

FAMILY II.—*Tonics*, drugs which so influence nutrition as to increase the reconstruction or upbuilding of the tissue or tissues concerned.

FAMILY III.—*Alteratives*, drugs which so modify nutrition as to overcome certain chronic pathological processes.

FAMILY IV.—*Antiperiodics*, drugs which so modify nutrition as to overcome the effects of malarial poisoning.

FAMILY V.—*Antipyretics*, drugs which so modify nutrition as to overcome febrile movements.

CLASS II.—LOCAL REMEDIES, drugs which affect one organ or apparatus more or less isolated from the remainder of the body.

FAMILY I.—*Stomachics.**
" II.—*Emetics.*
" III.—*Cathartics.*
" IV.—*Diuretics.*
" V.—*Diaphoretics.*
" VI.—*Expectorants.*
" VII.—*Emmenagogues.*
FAMILY VIII.—*Oxytocics.*
" IX.—*Counter-irritants.*
" X.—*Escharotics.*
" XI.—*Demulcents.*
" XII.—*Emollients.*
" XIII.—*Protectives.*

EXTRANEOUS REMEDIES.

FAMILY I.—*Antacids.*
" II.—*Anthelmintics.*
" III.—*Digestants.*
FAMILY IV.—*Absorbents.*
" V.—*Disinfectants.*

* The definitions are not given in these families, as they are old and well known and their names show the reader to what organs each applies. It should be stated, however, that the family *stomachics* contains drugs which are used simply as stimulants to the gastro-intestinal tract, including, therefore, *Simple Bitters*, so called, and *Aromatics*.

DIVISION I.—SYSTEMIC REMEDIES.

CLASS I.—GENERAL REMEDIES.

ORDER I.—NERVINES.

FAMILY I.—ANTISPASMODICS.

UNDER the name of *Antispasmodics* are grouped in this treatise a number of medicines generally of very feeble powers, but of frequent use. In certain conditions of the nervous system—conditions associated with weakness rather than with simple depression—the nerve-centres appear to be more susceptible than is normal to external impressions, as well as to those impulses which originate in the cerebral centres themselves and are connected with the emotions. As a result of this state, various symptoms arise, of trifling import, but often apparently severe, and always annoying. Such symptoms, in their mildest form, constitute the state of unrest known as *nervousness;* in their severer type they may rise in intensity up to the wildest convulsion of *hysteria.* It is in this class of affections that the so-called antispasmodics are useful. As the condition which they relieve is always associated with weakness, they are often spoken of as "nerve-stimulants." In regard to most of them there is but little evidence of their increasing power or functional activity when administered to healthy individuals. Some of them act slightly upon the circulation when given in very large doses, and a few when administered as freely as possible induce slight cerebral symptoms, such as vertigo; but, except camphor and Hoffmann's anodyne, none are capable of producing serious poisoning. As any theory of the method in which the hysterical convulsion originates —of its immediate causes and the mechanism of its production—would, with our present knowledge, be at best but an ingenious speculation, the safest plan in regard to the action of drugs belonging to the class now under consideration is to accept the teachings of clinical experience as to facts, and to avoid theorizing as to the way in which the results are brought about.

MOSCHUS—MUSK. U. S.

A highly odorous, unctuous substance, obtained from the glands situated just in front of the preputial orifice of the Moschus moschiferus, or musk-deer of Thibet. The genuine musk-sac is to be distinguished from

imitations of it by the hairs being arranged concentrically around a minute orifice. As it occurs in commerce, musk is very greatly adulterated.

PHYSIOLOGICAL ACTION.—Musk appears to act upon the nervous system simply as a mild stimulant and antispasmodic. Jörg and Sundelin have experimented with it upon healthy men with somewhat contradictory results. According to the first-named observer, twenty grains of it induce exhilaration without lassitude, but, according to the latter authority, may cause giddiness, drowsiness, and lassitude. Both observers noted a slight increase in the frequency of the pulse.

THERAPEUTICS.—Musk is at present very little used, but it is strongly recommended by some of the older writers in various spasmodic affections, especially in *hysterical convulsions*. In *hiccough* it has been considered a specific. In our experience, in the crisis of low fevers when the symptoms of nervous exhaustion are extreme and threaten death, musk is a very valuable remedy. Thus, in advanced *typhoid fever* a condition sometimes develops in which the pulse is exceedingly feeble, and the temperature has a tendency to rise to a great height, but yields almost immediately to the use of cold, only, however, to remount as soon as the cold is withdrawn. We have seen musk at such time control the temperature, steady the pulse, and apparently save life. In other cases of advanced fevers the powers of the system entirely give out, and the patient passes into a condition of collapse, with subnormal temperature, and mayhap coma-vigil: this state we have also seen relieved by musk. Originally recommended by Trousseau in the *ataxic pneumonia* of drunkards, musk may be a useful remedy in any forms of *adynamic pneumonia* when there is wild or muttering delirium. From ten to fifteen grains of musk (the best attainable) must be given at a dose, preferably by rectal injection, suspended in mucilage. The effect of the single dose lasts about six hours. The dose of the Tincture of Musk (TINCTURA MOSCHI—five per cent., U. S.) is from one to two fluidrachms (4–8 C.c.).

VALERIANA—VALERIAN. U.S.

The root of the Valeriana officinalis, an herbaceous perennial of Europe. It consists of a short, yellowish-white rhizome, with numerous fibrous roots, of a bitter taste and peculiar odor. Valerian depends for its activity upon a volatile oil and the valerianic acid which it contains.

PHYSIOLOGICAL PROPERTIES.—The physiological action of valerian is very feeble. The extraordinary excitement which it produces in cats is probably due to a suggestive odor rather than to any direct influence. Large doses of valerianic acid cause in rabbits some acceleration of the pulse and respiration, followed by lessened frequency of these functions and general lassitude. Enormous doses may produce a fatal gastric enteritis. According to Butte,[1] the extract of valerian has a pronounced effect in checking the destruction of glucose in the blood.

Upon man, very large doses (ʒii to ʒiv) are said to produce a feeling

of warmth in the stomach and quickening of the pulse, followed by nausea, vomiting, and colicky pains.

THERAPEUTICS.—Valerian is useful in the state of unrest familiarly known as *nervousness*, is much used in the minor disturbances of *hysteria*, and has been employed, though with little advantage, in *mania a potu* and *adynamic delirium* as an adjuvant to more powerful drugs. The dose of the fluid extract (EXTRACTUM VALERIANÆ FLUIDUM, U. S.) is one fluidrachm (4 C.c.); of the ammoniated tincture (TINCTURA VALERIANÆ AMMONIATA—twenty per cent., U. S.), one to three fluidrachms; of the simple tincture (TINCTURA VALERIANÆ—twenty per cent., U. S.), one to three fluidrachms (4–10 C.c.).

AMMONII VALERIANAS. U. S.—Ammonium valerianate is a white salt occurring in quadrangular plates, which effloresce in a dry and deliquesce in a moist atmosphere, have the odor of valerianic acid and a sharp, sweetish taste, and are very soluble in water and in alcohol. According to W. E. Parke,[2] it produces in the frog convulsions followed by general paralysis, both the convulsions and the palsy being of spinal origin, and also is capable by local contact of killing any of the higher nerve-tissues. These effects are probably due to the ammonia, and throw no light upon the therapeutic action of the drug, which is about equivalent to valerian, but sometimes has especial usefulness in *nervous* headache. Dose, ten grains (0.65 Gm.), generally administered in the form of an *elixir*.

ASAFŒTIDA—ASAFETIDA. U. S.

An exudation obtained by incising the living root of the Ferula Narthex, an umbelliferous plant of Afghanistan. It occurs mostly in irregular opaque masses of a dull yellowish or pinkish brown, white when freshly broken, of a bitter acrid taste and a strong garlicky odor. Even this *lump asafetida* is largely composed of tears agglutinated together; sometimes these tears are distinct and separate, when they constitute the variety known as *asafetida in tears*. Asafetida is composed chiefly of gum and resin, but its properties are in great part due to the volatile oil, of which it contains from 3.5 to 4.5 per cent.

PHYSIOLOGICAL ACTION.—When taken into the stomach, asafetida acts as a local stimulant and carminative, and on this account is in some parts of the East used as a condiment. The oil is without doubt absorbed. The evidence as to its action upon healthy men is both scanty and contradictory. Thus, while M. Pidoux took half an ounce in a single dose without perceptible effects other than to render his secretions horribly offensive for two days, Jörg and his disciples found that in twenty-grain doses it produced gastric uneasiness and pain with alvine dejections, increased the pulse-frequency and animal warmth, quickened the respiration, and caused headache, giddiness, and erotic excitement.

THERAPEUTICS.—Asafetida is the most efficient of the minor antispasmodics, and may often advantageously be substituted for valerian in *func-*

tional spasm, in *hysteria*, and in *nervousness*. It differs from valerian in having a much more decided action upon the mucous membranes. It is an excellent *carminative*, and in the form of injection is constantly used for the relief of *tympanites*. It is valuable in the *dyspepsia*, with flatulent colic and costiveness, of the aged or hysterical. As a *stimulating expectorant* and *antispasmodic*, it is useful in *whooping-cough* and in *chronic bronchial catarrh*, especially in old people with an asthmatic tendency. In *infantile convulsions* and in *severe infantile colic*, asafetida enemata (f℥ii to f℥ss of the milk) are exceedingly useful and harmless.

DOSE.—Dose of the Pills of Asafetida (PILULÆ ASAFŒTIDÆ, U. S., three grains each), two to four; of the mixture or milk of asafetida (EMULSUM ASAFŒTIDÆ—four per cent., U. S.), half to one fluidounce (15–30 C.c.), or for injections, one to eight fluidounces (30–240 C.c.); of the tincture (TINCTURA ASAFŒTIDÆ—twenty per cent., U. S.), half to one fluidrachm (2–4 C.c.).

CAMPHORA—CAMPHOR. U. S.

Camphor is obtained in China, Japan, Cochin China, the Sunda Islands, etc., by boiling the comminuted wood of the root, stem, and branches of the Laurus Camphora, and skimming off the camphor as it rises to the surface of the water when cooled. This camphor is then partially purified by sublimation, and comes into commerce as *crude camphor*, which is in grains of a whitish or pinkish color, and is finally purified by sublimation with lime.*

Refined camphor (or, as it is commonly called, *camphor*) occurs in disks or hemispherical bowl-like translucent masses, of a fibrous or granular fracture. Its taste is hot and peculiar; its odor very strong and characteristic; it is volatile, inflammable, tough, but readily pulverized on the addition of a few drops of alcohol; melts at 347° F.; is soluble in one thousand parts of cold water,† in one part of strong alcohol, and still more soluble in chloroform; thrown upon water, a granule of camphor floats, and exhibits a rotatory movement.

PHYSIOLOGICAL ACTION.—Locally applied, camphor is a decided irritant, although when it is taken into the mouth a sense of coolness after a time is experienced, due no doubt to the volatility of the drug; a precisely analogous phenomenon occurs with some other volatile irritants, such as oil of peppermint.‡

Great differences of opinion have prevailed in regard to the action of camphor upon man, and it is scarcely doubtful that it acts differently upon

* Borneo camphor, yielded by the Dryobalanops Camphora, is very highly valued in the East, but does not reach this country. Stockman has found that both it and the *Ngai camphor* of China act on the organism like camphor. See also Paolo Pellicani, *Arch. f. Exper. Pathol. und Pharm.*, xvii. 376.

† By rubbing the camphor up with magnesia in water, the latter can be made to take up much more than one part in one thousand.

‡ For the physiological action of camphor-cymol, see *Arch. f. Exper. Path. und Therap.*, 1873, i.

different persons, or at least that doses which in some cause only exhilaration produce general depression in others. When a moderate dose (five to ten grains) of camphor is taken, a feeling of exhilaration is usually induced, a sense of comfort and quietness, especially marked in those previously suffering from "nervousness;" the pulse may be somewhat accelerated, although it is undoubtedly not markedly affected in the majority of cases, and Trousseau saw it fall after the ingestion of ten grains of the drug. After larger doses (twenty to thirty grains) the pulse is usually lowered in frequency, and giddiness, with a feeling of lassitude, is produced, preceded, it may be, by a short period of exhilarative excitement. After poisonous doses (thirty to sixty grains) the symptoms, which are tolerably uniform, are as follows: faintness, headache, vertigo, confusion of ideas, burning pain in the stomach, delirium, spasms deepening into violent convulsions, insensibility, general paralysis; pulse at first full and quick, but later small and sometimes slow; skin cool, pale or livid, generally bedewed with sweat. Sudden unconsciousness, with or without convulsions, has been in some instances the first manifestation of the action of the poison, and, of course, in any individual case many of the symptoms detailed above may be wanting.*

The only fatal poisonings that we know of are: adult, quantity unknown;[1] sickly infant, ten grains;[2] child two years old, unknown amount;[3] fatal abortion produced by three drachms.

Although it has been frequently stated that camphor produces sexual excitement, we have never been able to perceive that the moderate dose exerts any influence whatever upon the genital organs. In very large doses it is believed by many to lessen erotism, but even this action is very uncertain.

Camphor acts upon articulates as a violent poison; in birds, according to Menghini, it causes stupor or delirium with epileptiform seizures; in mammals it produces symptoms similar to those seen in man, such as vomiting, violent convulsions, coma, and death, apparently from asphyxia. The convulsions must be of cerebral origin, as, according to C. Weidemann[4] and Hoffmann (quoted by Weidemann), they do not occur after section of the cord in portions of the body below the point of division.

The cerebral symptoms in camphor-poisoning indicate that the drug has a depressing influence upon the cerebral cortex and that the epileptic convulsions produced by it are probably cortical in their origin, a conclusion which is strongly confirmed by the research of R. Stockman,[5] who found that after removal of the cerebral cortex in the rabbit camphor did not produce convulsions. As was first shown by Weidemann, and later by Stockman, toxic doses of camphor in the frog produce paralysis of the motor nerves, the muscles retaining their functional power. That this loss

* Cases, *Edinburgh Med. Journal*, May, 1873; *The Clinic*, March, 1873; *Wiener Medizinische Presse*, 1874, 258; *Berlin. Klin. Wochens.*, Sept. 1873–74; *Trans. Lond. Clin. Soc.*, 1874, 27; *London Lancet*, 1876, ii. 71; *Brit. Med. Journ.*, Feb. 1875, 1877, i. 607, Sept. 1895; *St. Petersburg Med. Wochens.*, 1897, xiv.

of nerve-power is not the sole cause of the motor disturbance is, however, shown by the fact that spinal reflexes persist in the poisoned frog long after voluntary movements have ceased, and that great lessening of the reflex activity always occurs before the motor nerves show any falling off in their excitability. All investigators are in accord in believing that finally in camphor-poisoning there is centric paralysis of the spinal cord, but both Binz[6] and Grisar[7] believe that a stage of spinal stimulation precedes the depression. The later experiments of Stockman, however, throw great doubt upon this.

In the experiments of Cesare Rossi,[8] made with a Mosso's ergograph, camphor sometimes seemed greatly to increase the energy and endurance of the human muscles, but in other cases failed to have any influence ; it may be that it is a general muscle-stimulant.

The action of camphor upon the circulation is decided, although our knowledge of it is incomplete. The moderate dose acts directly as a stimulant to the heart-muscle, since Heubner[9] has found that camphor is able to excite the heart when arrested by muscarin, and Heubner, Harnack, Wittkowski,[10] Weidemann, Umpfenbach,[11] Maki, and Stockman all agree in asserting that though the drug decreases the rate it markedly increases the energy of the contractions of the isolated frog's heart. The contrary results of Alexander Lewin[12] were due to the use of overwhelming doses, camphor first stimulating and then depressing the heart-muscle.

The action of the drug upon the circulation in the mammal is complicated, and our knowledge concerning it not yet perfect. It appears to be proved that the toxic dose lessens the arterial pressure both before and after section of the spinal cord, probably by a paralytic action upon the heart and also upon the arterial system. As is shown by Weidemann, during the convulsive stage of camphor-poisoning there is a marked rise of the arterial pressure, which, however, may be prevented in great measure by curarization and artificial respiration, and is therefore evidently chiefly due to the convulsions and disturbances of breathing. In the curarized animals, however, curious sudden periodic elevations of the arterial pressure occur, the cause of which remains unknown. According to Weidemann, they are prevented by section either of the cord or of the vagi ; and Stockman found that, at least with Borneo camphor, they were very inconstant. The conclusion of Stockman, that the failure of camphor to elevate the arterial pressure is due to its depressing the vaso-motor centre in the medulla and thereby producing a vascular dilatation which masks the increased action of the heart, is probably correct. It is confirmed by the fact that both Maki and Lewin have found that camphor in deeply chloralized animals, when the vaso-motor centres are paralyzed, elevates the blood-pressure. Our present knowledge indicates that camphor in small dose directly stimulates the heart and widens the blood-paths by a centric depression, and that in toxic dose it depresses both the heart and the arterial system.

According to Stockman and Binz,[13] camphor increases the rate of res-

piration greatly ; and Lewin found that the amount of respired air moved was greatly increased in the rabbit by it ; so that camphor is probably a central respiratory stimulant.

Camphor is undoubtedly very much changed in the organism; the most important of its derivatives is *campho-glycuronic acid*,* discovered in the urine by Schmiedeberg and Meyer.[14] Glycosuria has been noted by Stockman in camphor-poisoning.

THERAPEUTICS.—Camphor is very frequently used internally as an antispasmodic, to quiet restlessness and "*nervousness*." It is also employed in certain painful affections seen in those persons who are especially liable to the condition of the nervous system just mentioned : thus, it is often useful in *nervous headaches* and *dysmenorrhœa*. Indeed, in the latter disease, either alone or combined with opium in bad cases, it is a most valuable drug, but must be given freely. In *diarrhœa* not dependent upon inflammation, in *nervous diarrhœa*, in *cholerine*, and even to some extent in *cholera*, camphor is an efficient remedy, allaying intestinal pain and spasm, and also checking intestinal secretion. It enters into a large proportion of the popular cholera-mixtures. In sudden *cardiac failure* and in *adynamic conditions* it is much used in Germany, but in this country is rarely employed either as a cardiac or general stimulant. According to Schilling, thirty grains a day may be given hypodermically † in the profound adynamia of acute *endocarditis*, *typhoid fever*, *pneumonia*, etc., with the happiest result. The use of large doses of camphor in *abnormal sexual excitement*, and in *chordee*, has about passed out of vogue, which also is true of its employment in severe convulsive disorders such as *whooping-cough*, *epilepsy*, and *puerperal convulsions*. In *hysterical convulsions*, as in other phenomena of similar origin, camphor is a useful antispasmodic.

Externally, camphor is much used in liniments as a stimulant application for *bruises*, *sprains*, etc.

ADMINISTRATION.—Large doses (ten to fifteen grains) of camphor are best administered in emulsion, because when given in this way, being very finely subdivided, they create as little irritation as possible, and are rapidly absorbed ; smaller doses may be given in pill. As an antispasmodic, the Camphor Water (AQUA CAMPHORÆ—eight-tenths of one per cent., U. S.) is usually preferred ; its dose is half a fluidounce to two fluidounces (15–60 C.c.), but, when a decided effect is desired, the Spirit of Camphor (SPIRITUS CAMPHORÆ—ten per cent., U. S.) is more effective ; its dose is fifteen to thirty minims (1–2 C.c.). For external use are official the LINIMENTUM CAMPHORÆ (camphor one part, cotton-seed oil four parts, U. S.) and the LINIMENTUM SAPONIS, or Soap Liniment, U. S.,—a mild liniment, very popular either by itself or as the basis of more stimulating preparations.

* For a physiological study of campherol, a derivative of campho-glycuronic acid, see *Archiv f. Exper. Path.*, xvii. 372.

† The preparation used is a ten per cent. solution in olive oil.

The *Oil of Camphor* occurs in our market as a reddish or yellowish-brown liquid, having a strong odor of camphor, and a hot, camphoraceous taste. It contains camphor in solution, and is probably equivalent to it in physiological action, except that it is locally more stimulating, and preferable in intestinal disorders. Dose, five to ten drops (0.3–0.6 C.c.).

CAMPHORIC ACID.—This is produced by boiling camphor with concentrated nitric acid. It occurs in small white, acicular or scaly crystals, free from odor, of a feebly acid taste, sparingly soluble in cold, freely in hot, water, also in alcohol, ether, and fatty oils. It was originally proposed by Fürbringer[1] as an antiseptic of practical value for the disinfection of the intestinal canal and in the treatment of *tuberculosis* and ammoniacal *cystitis:* as first noticed by Wittkowski it is a very valuable antihidrotic in the *night-sweats* of *phthisis;* how it acts in these cases has not been determined. Max Reichert, Niesel, and other physicians have found it very serviceable as a local application in the treatment of tubercular and other *catarrhs* of the upper and lower air-passages.

According to Bohland,[2] camphoric acid is rapidly eliminated, the whole of a single dose escaping from the kidneys in the course of five hours unaltered. In *cystitis*, fifteen grains (1 Gm.) may be given three or four times a day; for *night-sweats*, fifteen to thirty grains may be given at bedtime, or, when the sweat occurs late in the night, the dose may be divided, the patient being wakened to take the last dose after midnight. Gastric irritation and even vomiting have been noted after thirty grains, and Niesel saw severe renal irritation in a patient who had taken in four weeks fifty grammes.

CAMPHORA MONOBROMATA. U. S.—*Monobromated Camphor* or *Bromated Camphor.*—With iodine and bromine camphor unites to form compounds. According to Laurent, *bromcamphor* occurs in red orthorhombic crystals. These when exposed to the air undergo rapid spontaneous decomposition, but by heating in a closed vessel are resolved into hydrobromic acid, and a compound in which one atom of hydrogen in the camphor has been replaced by bromine. This bromated camphor is a crystalline solid, or occurs in large acicular crystals several inches long.

Our present knowledge of the physiological properties of bromated camphor rests upon the work of Bourneville,[1] of Lawson,[2] of Pathault,[3] of Richard Peters,[4] and of Pellicani.[5] In frogs there is progressive loss of reflex excitability and of voluntary movement (Peters), which, according to Pellicani, is due to paralysis of the motor nerves. Death is caused by arrest of respiration (Peters). In mammals it produces violent convulsions, muscular weakness passing almost into paralysis, reduction of temperature (after small doses preceded by a rise—Peters), great decrease in the rate of the respiration and of the pulse, with occasional periods of hurried respiration (Peters), profound sleep or stupor, and finally death. Bourneville states that the blood-vessels of the eyes and ears are dimin-

ished in calibre. Upon man the drug probably acts as upon other warm-blooded animals; in a case reported by M. Rosenthal,[6] forty-five grains of it caused tremblings, marked slowing of the pulse, and coma of six hours' duration.

Bromated camphor was first introduced by Deneffe[7] as a nervous sedative, and as an antispasmodic, especially in *delirium tremens*, but is of little value; it is still used in *hysteria*, and has an especial reputation in *sexual excitement* and *spermatorrhœa*. It is taken with difficulty, and is apt to irritate the stomach. It is too irritant for hypodermic use. Dose, five to ten grains (0.3–0.6 Gm.), in capsule or coated pill, and repeated as necessary.

SPIRITUS ÆTHERIS COMPOSITUS—COMPOUND SPIRIT OF ETHER. U.S.

Hoffmann's Anodyne consists of 325 parts (by volume) of ether, 650 parts of alcohol, and 25 parts of ethereal oil. It is a colorless, inflammable liquid, of an aromatic, ethereal odor, and a burning, slightly sweetish taste. Its specific gravity is 0.815. SPIRITUS ÆTHERIS, U.S., which contains no ethereal oil, is often improperly sold under the name of Hoffmann's anodyne. It can be distinguished at once by the fact that forty drops of the genuine preparation will render a pint of water distinctly milky, whilst the simple spirits of ether has no such effect. Ethereal Oil (OLEUM ÆTHEREUM, U. S.) is a transparent, nearly colorless, volatile liquid, of a peculiar aromatic odor and a sharp, bitter taste. Its specific gravity is 0.91. It is *heavy oil of wine*, prepared by the action of an excess of sulphuric acid on alcohol, and diluted with an equal part of strong ether.

PHYSIOLOGICAL AND THERAPEUTIC ACTION.—H. A. Hare found that the *heavy oil of wine* caused a rise, followed, if the dose were large enough, by a very marked fall both of the pulse-rate and of the arterial pressure. As the primary rise in the arterial pressure did not occur after section of the spinal cord, it must be, at least in large part, due to stimulation of the vaso-motor centre. The fall of pressure is probably in part the outcome of a direct depressant action of the drug upon the heart, since that viscus finally suffers diastolic arrest; but, as in the earlier period of lowered pressure the individual heart-beats were extremely full and strong, it is probable that vaso-motor paralysis precedes cardiac depression and causes the lowered pressure by widening out the blood-paths. This vaso-motor palsy Hare believes to be chiefly of peripheral origin. In his studies upon frogs, Hare failed to detect any indication of an action of the oil upon the spinal cord, nerves, or muscles. He found the toxic properties of the heavy oil of wine to be very feeble; thirty cubic centimetres given by the mouth to a small dog (weight twelve pounds) failed to produce marked symptoms. It is therefore evident that the small quantity of the heavy oil of wine contained in Hoffmann's anodyne can exert no very pronounced influence upon the human system, and that the effect of Hoff-

mann's anodyne is chiefly that of ether and alcohol combined. Clinical experience indicates, however, that Hoffmann's anodyne is more calmative than the simple combination of ether and alcohol. It is a very efficient carminative, and is also a useful antispasmodic in all the disorders for which such remedies are employed, especially when there is a tendency to failure of the circulation ; in *valvular cardiac disease* it is often very effective in relieving mild heart-pains. The dose is one to two fluidrachms (4–8 C.c.), repeated in half an hour or an hour, if required, and given in cold water.

HUMULUS—HOPS. U. S.

The strobiles of Humulus Lupulus, or the hop-vine, cultivated in Northern and Middle Europe and in the United States. Hops are soft, greenish cones, one or two inches in length, composed of thin, leaf-like, imbricated scales, having a bitter taste and a heavy narcotic odor. At the bases of the scales is a yellowish powder, official under the name of *Lupulinum*. *Lupulin* is in minute grains, and contains, according to Payen, two per cent. of volatile oil, 10.30 per cent. of bitter principle, and fifty to fifty-five per cent. of resin. Volatile oil of hops is yellowish, and has a strong odor of the drug and an acrid taste. The bitter principle has been obtained by Lermer in brilliant rhombic columns, of an acid reaction.

Hops is a bitter tonic and a very feeble narcotic, which has been given to quiet nervous irritability, and to strengthen digestion in *neurasthenia*, and even in *delirium tremens*. In *abnormal sexual excitement* it has been much used, but is of no value. Dose of the tincture (TINCTURA HUMULI—twenty per cent., U. S.), half a fluidounce to three fluidounces (15–90 C.c.) ; the oleoresin of Lupulin (OLEORESINA LUPULINÆ, U. S.), ten minims to a fluidrachm (0.6–4 C.c.), in capsules if desired ; the fluid extract (EXTRACTUM LUPULINÆ FLUIDUM, U. S.), half a fluidrachm to two fluidrachms (2–8 C.c.).

A *hop poultice* is made by moistening with hot water the hops contained, alone or mixed with an equal part of Indian meal, in a gauze bag of the required size and shape.

CIMICIFUGA—BLACK SNAKEROOT. U. S.

The root of Cimicifuga racemosa, an indigenous herbaceous plant, growing abundantly in shady woods, attaining a height of six or seven feet, and readily distinguished by its very large multi-compound leaves and its long-branched spikes of whitish polyandrous flowers, naked when open. The root consists of a knotted head, with numerous fine, brittle rootlets ; the odor is faint, and the taste bitterish, somewhat astringent and acrid. The nature of its active principle has not been determined. Commercial *Cimicifugin* or *Macrotin* is an amorphous resinous substance. The tendency of the drug to deteriorate on keeping would indicate the presence of a volatile principle.

PHYSIOLOGICAL ACTION.—There have been no cases of poisoning by it, but large doses produce giddiness with intense headache and general prostration (evidences that it has influence upon the cerebrum), with reduction of the pulse-force and rate, and occasionally vomiting, but its emetic action is never violent. That the overdose of cimicifuga has physiological activity is shown by the experiments of Hutchinson,[1] who found that in frogs it acts as a depressant of the sensory side of the spinal cord, producing complete anæsthesia with loss of reflex activity at a time when voluntary movement is still preserved, the development of the anæsthesia not being prevented by shutting off access of the poison from the peripheral nerves by tying the arteries of the leg, and both motor nerves and muscles being found after death functionally active. Upon the circulation cimicifuga acts as a depressant, producing in the mammal fall of the arterial pressure and slowing of the pulse, and causing finally diastolic arrest of the heart. As the slowing of the pulse is not prevented by previous section of the vagi, and as the isolated frog's heart becomes slow and in a little while paralyzed after direct contact with the cimicifuga, it is evident that the drug acts as a direct depressant to the heart-muscle ; but, since Hutchinson found that asphyxia is incapable of causing rise or pressure while the heart is still beating strongly, it is probable that it not only depresses the heart but also the arterial system. Under the influence of the drug the respiration becomes slow and suffers final arrest.

THERAPEUTICS.—Cimicifuga was originally proposed by Young[2] in 1831 as a remedy in *chorea*, and in the simple chorea of childhood its value is unquestionable. It must be given until it produces physiological effects, and in most cases the consentaneous exhibition of iron and laxatives materially aids it. We have seen it promptly cure *urticaria* of nervous origin after complete failure of the usual treatment. In acute *inflammatory rheumatism* cimicifuga has been highly recommended, but is at present very rarely, if ever, used. In *chronic bronchitis* it is sometimes employed with asserted benefit when there is free expectoration.

ADMINISTRATION.—The best preparation is the fluid extract (EXTRACTUM CIMICIFUGÆ FLUIDUM, U. S.) ; dose, from twenty minims to a fluidrachm (1.2–4 C.c). Tincture (TINCTURA CIMICIFUGÆ—twenty per cent., U. S.); dose, one to two fluidrachms (4–8 C.c.). EXTRACTUM CIMICIFUGÆ, U. S. ; dose, five to twenty grains (0.3–1.3 Gm.).

LACTUCARIUM. U. S.—The concrete juice of the Lactuca virosa,* or garden lettuce, occurs as a dark reddish-brown to a light yellowish, hard extract, having a faintly narcotic odor and bitter taste. A peculiar soothing, hypnotic influence has been attributed to it, but its activities are so feeble that in a number of trials with very large doses we have been unable to perceive any effect whatever. According to Fronmüller,[1] *lactucin* is even less active than the crude drug. In France lactucarium is used

* For a case of reputed poisoning by Lactuca virosa, see *Schmidt's Jahrb.*, clxxi. 137.

locally as a narcotic demulcent in the treatment of diseases of the throat. The usually assigned dose of lactucarium is thirty grains (2 Gm.), that of the fluid extract (EXTRACTUM LACTUCARII FLUIDUM) half a fluidrachm (2 C.c.). TINCTURA LACTUCARII fifty per cent., U. S. ; dose, one to two fluidrachms (4–8 C.c.). SYRUPUS LACTUCARII—ten per cent., U. S.; dose, half to one fluidounce (15–30 C.c.). Much larger quantities may be given without effect.

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CAMPHORA MONOBROMATA.

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2. LAWSON . . . . . Practitioner, 1874, 1875.
3. PATHAULT . . . . Bromure de Camphor, Paris, 1875.
4. PETERS . . . . . S. Jb., ci. 126.
5. PELLICANI . . . . S. Jb., ci.
6. ROSENTHAL . . . S. Jb., ci. 127.
7. DENEFFE . . . . Presse M. B., 1871.

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1. HUTCHINSON . . Th. G., 1887, 731.
2. YOUNG . . . . . A. M. J. S., 1831, ix.

LACTUCARIUM.

1. FRONMÜLLER . . Deutsche Klinik, 1865.

FAMILY II.—ANÆSTHETICS.

THE term *Anæsthetics* is here employed as the name of a group of volatile substances, whose vapor has the power of producing loss of consciousness, preceded by or accompanied with loss of sensibility and diminished muscular action. The medical properties of these substances are largely due to their volatility, by virtue of which they are very rapidly absorbed and almost as rapidly eliminated by the mucous membrane of the lungs. As a consequence of this, their action is easily controlled.

A very large number of theories have been brought forward to account for the peculiar effects of anæsthetics; of the more important of these theories an elaborate discussion may be found in the tenth edition of this work. There is, however, nothing more mysterious in the action of ether and chloroform upon the nerve-centres than there is in the influence of opium or strychnine upon these centres, the influence of the anæsthetic being as certainly direct and vital as is that of any other drug which acts upon human organs or tissues.

The action of anæsthetics may be modified by the injection of narcotics. Morphine given hypodermically about half an hour before the exhibition of the anæsthetic is said to have a decided effect in prolonging the anæsthesia. Chloral administered shortly before etherization certainly causes the first stages of the latter to be much quieter than usual, and also prolongs the narcosis. Some years since Neudörfan[1] introduced into Berlin the use of oxygen gas with chloroform in the production of anæsthesia; more recently the method has been revived in America.* It has even been asserted that the oxygen increased the anæsthetic effect of the chloroform. There is not at present writing sufficient evidence, however, of the value of the method.

The chief purposes for which anæsthetics are used are to *relieve pain* and to *relax spasm*. To meet the first indication they are employed by surgeons especially; but they are also exceedingly valuable in cases of suffering from disease. It must be borne in mind that their action is transitory and is accompanied by more or less disturbance of the general system, and that consequently they are to be employed only when the pain is exceedingly severe and transient. To relieve pain, anæsthetics are used with great propriety during *childbirth*.† In natural labor it is not

* See *Boston Med. and Surg. Journ.*, 1896, and *New York Med. Record*, 1896.

† We see no reason for believing that anæsthesia of the mother seriously influences the child, and do not think that much weight can be attached to the assertions of Hofmeier (*Berlin. Klin. Wochensch.*, 1883, xx. 230) that there is produced an increased elimination of nitrogen in the new-born babe.

commonly necessary to produce complete anæsthesia. When the full effect of either ether or chloroform is induced, there is almost always a weakening, and very often an abolition, of the uterine contractions. The anæsthetic should be administered in such quantities as to relieve the pain without decidedly interfering with the muscular spasm. In certain cases this can be done, in others it is impracticable. We have obtained advantageous results in some cases by suspending the pains for about half an hour by means of ether, and then entirely withdrawing the anæsthetic. By this treatment the weak, painful, ineffectual efforts of a worn-out, nervous patient may often be converted into regular, successful efforts. The risk of *post-partum hemorrhage* is materially increased by anæsthetics, so that it is well to administer after their use two drachms of the fluid extract of ergot as soon as the perineum is well distended by the child's head.* Anæsthetics are frequently used in surgery for the purpose of relaxing spasm, as in cases of *dislocation*, *hernia*, etc. In medicine they have been employed in various forms of *convulsions*, and are especially valuable in severe *hysterical convulsions*, in *puerperal eclampsia*, and in *spinal convulsions;* in *epilepsy* they are very rarely called for; in *infantile convulsions* they may be sparingly used when the convulsion itself threatens life. In various *spasms* of the *excretory ducts* or *canals*, and especially during the passage of *calculi*, they act very favorably, both by relieving pain and by producing relaxation. In *asthma*, and in *spasmodic stricture* of the *œsophagus*, as in all other cases of oft-repeated spasm, they should be administered only to meet temporary indications, as their habitual use is deleterious.

NITROGEN MONOXIDE—NITROUS OXIDE.

Nitrous oxide is a colorless, almost inodorous, gas, of a sweetish taste. It is a very active supporter of combustion. Water absorbs nearly its own bulk of it. It is made by the distillation of ammonium nitrate, which resolves itself into the gas and water. Nitrous oxide gas is now supplied in condensed form. In making nitrous oxide the temperature should never be allowed to rise above 482° F., for fear of generating *nitric oxide*.

PHYSIOLOGICAL ACTION.—The inhalation of pure nitrous oxide gas is followed in from a half to three minutes by unconsciousness, which usually comes on quietly, but is sometimes preceded by hilarious, erotic, or pugnacious excitement. During the anæsthesia the face presents a bloated, swollen, intensely livid appearance.

The question whether nitrous oxide produces anæsthesia through inherent properties of its own, or whether it acts simply by shutting oxygen off, has been much discussed and variously answered.

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* Deaths from anæsthetics are very rare during parturition, but have occurred. (See C. B. Vanzant, *Cincinnati Lancet*, 1893, xxx.)

It is well established that nitrous oxide will not support life. A taper will burn in it, it is true, but the liberation of oxygen is due to the high heat, and at the temperature of the body nitrous oxide is a stable compound.

In 1864 Ludimar Hermann,[1] as the result of his experiments, came to the conclusion that the addition of oxygen to nitrous oxide puts an end to its anæsthetic properties, and that it acts simply as an asphyxiant. In 1873 MM. Jolyet and T. Blanche[2] arrived at the opinion that nitrous oxide has no direct effect upon the system, and that the narcosis is due to the lack of oxygen in the body; basing their conclusions upon the following facts experimentally determined by them: 1. Seeds will not germinate in nitrous oxide; 2. An animal lives no longer in nitrous oxide than in nitrogen; 3. Anæsthesia occurs at the time that the blood of an animal becomes black; 4. Animals breathing an air containing sixty to eighty per cent. of nitrous oxide and twenty to forty per cent. of oxygen are unaffected; 5. Analyses of the blood of two dogs yielded the following results:

No. 1. Conscious.		No. 2. Unconscious.	
Carbonic acid	46 per cent.	Carbonic acid	36.6 per cent.
Nitrous oxide	29 per cent.	Nitrous oxide	34.6 per cent.
Oxygen	19.7 per cent.	Oxygen	3.3 per cent.

And other analyses showed that the coma was not developed until the oxygen in the blood was reduced to three or four per cent.

The statements of the French observers just quoted have been abundantly corroborated by the observations of various subsequent investigators. Colton,[3] Elihu Thomson,[4] and H. C. Wood have separately and repeatedly demonstrated that animals will live no longer in nitrous oxide than they will in an atmosphere of hydrogen or nitrogen, or even in a vacuum. In a long series of experiments, H. C. Wood[5] found that two minutes and thirteen seconds were required to produce complete anæsthesia with pure nitrous oxide gas, while in mechanical asphyxia the same result was reached in two minutes and nine seconds. Thomson also asserts that in man the inhalation of pure nitrogen causes the symptoms of nitrous oxide narcosis. H. C. Wood further determined that the introduction of minute quantities of oxygen into nitrous oxide prolonged the time necessary for the production of anæsthesia in direct proportion to the percentage present, ten or even eight per cent. of oxygen suspending entirely the anæsthetic action of nitrous oxide gas upon the dog. The average time required for the production of anæsthesia was nearly doubled by the addition of three per cent. of oxygen, and increased more than twelvefold by the use of five per cent. of oxygen. An examination of the analyses of blood given above shows that the final loss of consciousness is not due to the presence of carbonic acid in the liquor sanguinis, since nearly ten per cent. more of that gas was present in the blood of the conscious (No. 1) than in that of the unconscious dog (No. 2), and also that it is more rational to believe that the decrease in the oxygen rather than the slight increase in the amount of the nitrous oxide made the difference between consciousness and unconsciousness. In conformity with this are the researches of C. A. MacMunn[6] and Amory; the former observer finding that when an animal is killed by nitrous oxide the arterial blood gives only spectrum lines of reduced hæmoglobin, while after death from chloroform the lines of oxyhæmoglobin are very apparent. Amory[7] demonstrated that during nitrous oxide narcosis the amount of carbonic acid exhaled from the lungs is only two-thirds of that eliminated before the inhalation, and that immediately after the recovery of consciousness less than one-third the normal amount of carbonic acid is given off. If the anæsthesia were due to the presence of carbonic acid in the blood, there should be during and immediately following the return of consciousness great increase in the elimination of this gas. It is evident, however, that during the whole narcosis little or no carbonic acid can be produced because

there is little or no oxygen in the blood ; and that consequently when the animal recovers consciousness there can be no pronounced elimination of carbonic acid until by the process of oxidation carbonic acid is formed.

As inert gases produce symptoms like those of nitrous oxide anæsthesia, as all these gases have in common with nitrous oxide the function when inhaled of shutting off the supply of oxygen, and as oxygen is necessary for the performance of life functions, it is natural to conclude that the shutting off of the oxygen by the nitrous oxide is the cause of the anæsthesia. It has been urged as an objection to this theory that the circulatory phenomena produced by the inhalation of nitrous oxide are essentially different from those of mechanical asphyxia.

It must, however, be borne in mind that the phenomena of mechanical asphyxia are largely due to the presence of an excess of carbonic acid in the blood, whilst in the asphyxia produced by nitrous oxide there is no excess of carbonic acid, so that the phenomena present are simply the outcome of a lack of oxygen. It is, therefore, *a priori*, to be expected that the symptoms of mechanical and of nitrous oxide asphyxia should differ to a certain extent. In an elaborate series of experiments H. C. Wood[17] found that the inhalation of nitrous oxide is usually followed by a rise of the arterial pressure, accompanied by a great disturbance of the pulse ; the pulse at first becoming irregular and tumultuous, but by and by settling, so that when anæsthesia is complete the pulse-wave is remarkably large and full and the rate very slow. The rise and fall of the arterial pressure in nitrous oxide anæsthesia was found to vary remarkably, not only in different inhalations, but at different periods of the same inhalation. Sometimes the rise was sudden, sometimes it was gradual ; sometimes it was maintained until near death, sometimes it was interrupted very early ; sometimes it was not very well marked, sometimes it was enormous. Dr. Amory[7] has found, in experiments with the cerebrometer upon the dog, that there is, during the anæsthesia, increased blood-pressure in the cerebrum, with stasis in the capillaries. These results show that the circulatory phenomena produced by nitrous oxide resemble those of mechanical asphyxia as closely as could, *a priori*, be expected.

Notwithstanding all the evidence which has just been given, there is much reason for believing that nitrous oxide has anæsthetic properties ; and that although the unconsciousness which is produced when pure nitrous oxide is inhaled is largely the outcome of the deprivation of oxygen, yet the drug is capable of producing narcosis by its own inherent properties.

Martin Goldstein[8] found that when he put frogs in an atmosphere of pure nitrous oxide they became motionless, with a complete loss of the reflexes, in fifteen minutes ; whilst when they were put in an atmosphere of nitrogen or some other indifferent gas they preserved their irritability for some hours. It is known that whilst the nervous system of the mammal requires for its activity the presence of oxygen, the nervous system of the frog remains functionally active for some hours after all circulation—that is, after all carrying of oxygen to it—has ceased.

Believing that if he could increase the amount of nitrous oxide in the blood he could get an anæsthetic action from it, Paul Bert experimented by exposing the animal in a chamber having air so compressed that the pressure was at least that of two atmospheres, and found that under these circumstances he could obtain anæsthesia with a mixture of eighty-five per cent. of nitrous oxide and fifteen per cent. of oxygen, but that when nitrogen was substituted for nitrous oxide no anæsthesia was produced. Bert's method was for a time employed for the purposes of surgical anæsthesia in Paris and in some other capitals of Europe, the clinical records showing that it is possible to produce anæsthesia with the gas in the pro-

portion named above. Practically, however, the necessary apparatus was found to be too cumbersome and expensive for use. In 1881 Klikovitch, of St. Petersburg, used with alleged success in parturition Paul Bert's mixture of gases without pressure.

In 1891 Van Arsdale[9] found that it was possible in rare cases to produce anæsthesia in the human being with mixtures of oxygen and nitrous oxide in the proportion of fifteen to eighty-five per cent., and that in many cases a mixture in the proportion of ten to ninety per cent. would produce a moderately complete anæsthesia without cyanosis.

In a research extending over three years, F. W. Hewitt[10] corroborated the assertions of Van Arsdale, finding that it is possible, in some cases at least, to produce deep and satisfactory anæsthesia, without obvious asphyxial manifestations, by mixtures of nitrous oxide and oxygen containing even as much of the oxygen as is present in our atmosphere. George T. Kemp[11] made a series of experiments, some of which seem to be very decisive. Thus, an animal having been anæsthetized with nitrous oxide, a slit in the canula was adjusted so that it let in just sufficient air to keep the animal alive and anæsthetized. When nitrogen was substituted for nitrous oxide, the amount of air remaining the same, the dog gradually came out of his anæsthesia. Experiments with the blood showed that, though at times perfect anæsthesia existed with as high a percentage of oxygen in the blood as 16.8, it usually was 8.5, and sometimes not until the percentage was reduced to 7.9. For reasons given in his paper, which we cannot go over here, Kemp believes that with this amount of oxygen metabolism remains about normal, a conclusion, however, which the evidence he brings forward hardly proves.

If nitrous oxide, as the evidence at present indicates, is capable of producing unconsciousness by virtue of its inherent properties, it must act upon the cerebrum, but it is remarkably inert in regard to other portions of the organism. The chief evidence as to its influence upon the spinal cord is that of Goldstein, that it diminishes the reflexes in frogs. That its action on the spinal cord is very feeble seems to be shown by the fact, which has been repeatedly asserted, that in human beings the conjunctival reflexes often persist after deep anæsthesia has been produced.

The experiments of Waller and of Amory show that nitrous oxide does not affect the motor nerve trunks. Ulbrich believes that it produces alterations in the blood, but Hermann, Jolyet and Blanche, Goldstein, MacMunn,[12] Buxton,[13] and Halliburton are in accord with Kemp in asserting that it does not make any compound with hæmoglobin. Further, Kemp is in accord with H. C. Wood's experiments in showing that it has no definite influence upon the heart or the arteries.

THERAPEUTICS.—Of all the anæsthetics, nitrous oxide is the safest. It is probably administered to more than seven hundred and fifty thousand persons yearly, and yet only four recorded deaths are certainly attributable to it.* The opinion of Cartwright[14] and of W. Ottley,[15] that in cases of heart disease permanent increase of the cardiac weakness is caused by nitrous gas inhalation, is not established. The final fall of blood-pressure produced by

* Not including the case reported in the *Dental Cosmos*, June, 1872. (See *Brit. Journ. Dent. Sci.*, Feb. 1873; *Brit. Med. Journ.*, 1877, i. 460; *Ibid.*, 1883, ii. 729; *Dent. and Surg. Microcosm*, Oct. 1895.) In one of these cases the result is said to have been due to syncope.

the gas was found in the experiments of H. C. Wood to be due to paralysis of the vaso-motor apparatus, probably of asphyxial origin, and death always occurred from respiratory paralysis, the heart continuing to beat powerfully after respiration had ceased and the arterial pressure had fallen very low. Even when alarming symptoms occur during nitrous oxide anæsthesia, the results are very rarely disastrous, because the loss of function has been due, not to the presence of a poison, but to the absence of oxygen, and although the paralysis may be complete, the life-power sleeps before it dies, and is ready to react to oxygen. *Immediate artificial respiration* is the *one remedy* for the treatment of alarming symptoms during nitrous oxide asphyxia.

In diseases of the kidney nitrous oxide is probably far safer than any of the liquid anæsthetics, since in the experiments of Thomson and Kemp [16] it was found to have no other effect upon the kidneys than that which it exerted upon the general circulation. Experience has not confirmed the assertion of Lafont, that nitrous oxide anæsthesia is prone to be followed by miscarriage, chlorosis, and epilepsy. His especial warning against the production of diabetes mellitus, and his statement that glycosuria may be produced by the drug in the dog, remain unconfirmed by clinical or experimental evidence, although a well-known Philadelphia surgeon persistently attributed his own fatal diabetes to the use of nitrous oxide. In experiments made by George S. Woodward and Alfred Hand in the laboratory of the University of Pennsylvania it was found impossible to produce glycosuria in the dog. On account of the high blood-pressure with venous stasis which occurs during nitrous oxide anæsthesia, atheroma or other diseases of the arterial walls should be considered a contra-indication to the use of the gas, and fatal apoplexy* has occurred during or immediately after its administration.

ADMINISTRATION.—The difficulty with the practical use of nitrous oxide for other than the brief anæsthesia required in teeth extraction and other forms of minor surgery has been the extreme fugaciousness of the anæsthesia, as well as the asphyxial symptoms always present. It is affirmed that these difficulties are overcome by the consentaneous use of oxygen with the gas. Undoubtedly the asphyxial symptoms are greatly lessened, but the allegation that the period of recovery after the withdrawal of the gas is distinctly prolonged has not, in our experience, been sustained. In various cases we have noticed the return to consciousness as complete in from twenty-eight to forty seconds. With great care in the administration of the mixed gases, the anæsthesia can be, it is true, almost indefinitely prolonged, but the danger of recovery at any moment is so strong that it is very doubtful whether the use of the mixed gases will ever prevail among surgeons.

The mixed gases have been employed in Philadelphia largely by one private operator and in the University of Pennsylvania Dental

* See *Dental Cosmos*, 1890; also *Therap. Gaz.*, 1896, xii.

Clinic. Independently the administrators of each place, after much experience, have fallen into the habit, as practically the best method, of giving first pure nitrous oxide and adding oxygen without any definite measurement when the asphyxial symptoms set in ; watching the effect of the oxygen and increasing or lessening it according to the facial expression of the patient. Matthew H. Cryer, of the University Dental Faculty, states that the apparatus prepared in London according to Hewitt's plan is impracticable owing to the fact that an easy reflux is afforded for the two gases into each other, and has worked out an apparatus which seems to be satisfactory and is not over-cumbersome. The method is certainly a distinct advance upon the older plan of giving nitrous oxide, in that it enables the operator at any moment to have the subject breathe pure oxygen if disagreeable symptoms occur.

ETHER—ETHYL OXIDE.

Ether is a colorless, very volatile liquid, obtained by the dehydration of alcohol by sulphuric acid. It is very inflammable, as is also its vapor, which is two and a half times heavier than air. It is freely soluble in alcohol, and is itself a powerful solvent. Its odor is strong and peculiar ; its taste is hot. Its specific gravity, when pure, is 0.713, and its boiling point 95° F. Ether of the U. S. Pharmacopœia should boil "when a test-tube, containing some broken glass and half filled with it, is held for some time in the hand."

Locally, ether is a violent irritant ; it is absorbed with rapidity through the mucous membranes both of the lungs and of the gastro-intestinal tract. When taken freely it is certainly eliminated in part unchanged.

Physiological Action.—The first effects of ether when inhaled are burning in the fauces and a feeling of strangulation, each due to the local impression of the irritant vapor. The primary indications of its systemic action are a sense of exhilaration and a lightness in the head, associated with a roaring or buzzing in the ears. These are soon succeeded by a feeling of the immediate surroundings being afar off, which soon fades into semi-unconsciousness, with visions and illusions. These are of various characters, and are often accompanied by a species of delirium. Some patients weep, others laugh ; some shout, some pray, some rave, and some become exceedingly pugnacious. In rare instances the dreams are erotic ; and cases are on record in which there were distinct evidences of the occurrence of a complete venereal orgasm. In this stage the patient in most cases may be more or less perfectly aroused. There is rarely sufficient anæsthesia for practical purposes before the period of complete unconsciousness.

The second stage of ether-narcosis may be considered to begin with the complete loss of consciousness. Muscular rigidity may persist for a length of time, but usually it soon passes off, and the patient lies relaxed

and quiet, with slow, regular, automatic respiration.* The occurrence of stertorous respiration, due to a paresis of the muscles of the palate, shows that the stage of muscular paralysis is being reached. It should, except in rare cases, be the signal for the immediate withdrawal of the anæsthetic.

The face during etherization is reddish ; marked pallor and lividity are respectively important indications of failure of the heart's action and failure of respiration. The stage of excitement generally lasts only a few minutes, but in some cases is prolonged, and in nervous women may pass into a violent fit of hysterics, which soon yields, however, to a persistent use of the anæsthetic. The pulse is quickened and increased in force by ether, and it will often maintain itself during a prolonged narcosis. If the vapor of ether be taken in a concentrated form, there is often in the beginning a momentary arrest of respiration, accompanied by a decided sense of suffocation, evidently the result of the irritant action of the vapor upon the upper air-passages. So soon as this has passed off, the respirations are usually accelerated as well as deepened ; but as the stage of anæsthesia is reached they become slower, and, if the inhalation of the ether be persisted in, they grow not only more and more distant, but also more and more shallow, until they are gradually extinguished.

The respiratory phenomena seem to be the same in the lower mammalia as in man. The primary arrest of respiration during the first stages of etherization is undoubtedly due to a local irritation of the mucous membranes of the air-passages. According to Kratschmer,[1] in the rabbit it is prevented by previous section of the trigeminal nerves, but not by division of the vagi ; nor does it occur when the ether is administered through a tracheal fistula. This would indicate that the respiratory disturbance is due to irritation of the peripheral trigeminal nerves, but H. A. Hare[2] has found that in the dog tracheal irritation with ether produces respiratory arrest, which is, however, prevented by previous section of the vagus. As stated by P. Knoll,[3] the arrest of respiration is sometimes replaced by very irregular breathing. The importance of the matter is increased by the fact that Kratschmer has noticed that the disturbances of respiration are accompanied by spasm of the glottis. It is evident that these disturbances are reflexes due to irritation of the trigeminal nerves in the upper, and of the pneumogastric filaments in the lower respiratory tract. They are especially interesting in connection with the asserted direct or indirect effect of ether upon the recurrent laryngeal nerve.†

It is possible, but not probable, that some of the accidents which have happened early in human anæsthesia have been due to these respiratory reflexes ; the important practical fact is that aberrations of respiration occur-

* For a full discussion of motor phenomena during profound anæsthesia, see Rudolf Jaksch (*Wien. Med. Wochensch.*, 1889, xxxix. 359).

† F. H. Hooper was, we believe, the first to note that stimulation of the recurrent laryngeal nerve causes a dilatation of the glottis in the thoroughly etherized dog, although in the normal animal it always produces a constriction. This remarkable observation has given rise to several investigations, the most extended of which is that of H. P. Bowditch (*Amer. Journ. Med. Sci.*, 1887, xciii.), to which the reader is referred for a full summary and discussion of the matter. Dr. Bowditch corroborates the observation of Hooper, and also finds that during partial etherization weak irritation of the recurrent nerves causes dilatation and strong irritation constriction of the glottis. As yet no satisfactory explanation of these curious phenomena has been offered.

ring in the beginning of an etherization are to be overcome by persistence in the inhalation, after which the respirations will become slower, deeper, and more regular ; indeed, as pointed out by Kronecker,[4] the late and dangerous arrest of respiration during anæsthesia occurs only after the reflex function has been abolished. When the administration is continued to the end, the respirations become very slow and more and more shallow until extinguished. Irregularities of respiration occurring in the later stages of an etherization are of the most serious import, and demand immediate withdrawal of the drug. Clinical experience confirms the experimental proof obtained by Knoll, that these late disturbances of respiration are the result of the direct influence of the drug upon the respiratory centres.

According to Eulenberg,[5] in the beginning of anæsthesia produced either by ether or by chloroform, the knee-jerk in man is increased ; when chloroform is employed, this increase soon disappears, but with ether it endures even into the narcosis.

Upon the lower animals ether acts as upon man, and it has been shown by Claude Bernard[6] that the most primitive infusoria are susceptible to its influence.

Both in man and the lower animals the cerebral functions are the first to be affected by ether. According to the experiments of H. C. Wood, Jr.,[7] when the ether is given in such a manner to the dog as to avoid all violence of administration, and in minute dose, the first positive indication of the loss of intellection is failure of the perception and interpretation of sound, the sense of sight lasting somewhat longer. Loss of coördination and loss of motor power, though with a continuation of movement, are the next phenomena. It was further demonstrated in these experiments that there is a stage of ether narcosis in which the sensibility is distinctly lessened, although no motor changes are demonstrable. This affords confirmation of the early experiments of Flourens,[8] who found that the order in which during etherization the power of responding to pricking is lost was, first, in the posterior or sensory portion of the spinal centres ; second, in the anterior or motor portions of the spinal cord ; and, third, in the medulla oblongata. Longet[9] has confirmed this order, except that by using powerful galvanic currents he was able, even in the deepest narcosis, to get a response from the anterior portion of the cord.

The order of the involvement of the nerve-centres in man and animals is—first the cerebrum, next the sensory centres of the cord, next the motor centres of the cord, next the sensory centres of the medulla oblongata, and finally the motor centres of the medulla oblongata.

Waller[10] found that if he brought dilute ether or chloroform vapor in direct contact with a motor nerve, that nerve lost its power of transmitting electrical impulses. If the vapor had not been too concentrated, the nerve recovered its function after removal of the anæsthetic. The recovery after chloroform was less rapid than after ether. If the observations of Longet (*loc. cit.*, 382) and Serres[11] be correct, the sensory nerve-fibres

are more susceptible to the influence of ether than are the motor. They found it possible, however, by the direct application of ether to a nerve, to produce a condition in which pinching the nerve below the point of application caused no pain, although voluntary movement was preserved, and galvanization of the nerve-trunk above the point of application induced spasms in the tributary muscles,—*i.e.*, the power of conducting an impulse downward was preserved, that of conducting it upward was lost. By a longer application of the anæsthetic the function of the efferent as well as of the afferent fibres was abolished, temporarily at first, but, if the application were persisted in, permanently.

Owing to the great sensitiveness of the nerve-centres in man, most if not all of the phenomena of etherization are of centric origin. Indeed, Conly [11] found that in animals killed by ether, chloroform, or chloral, the motor nerves and muscles preserve their function longer than in animals killed by sudden violence. Nevertheless, F. S. Locke [12] found that in the frog, at least, the muscles are directly affected by etherization ; there being not only a lessening of the height of the contraction under stimulation, but also an alteration in its form.

Upon the motor system of organic life ether certainly acts, but much less energetically than upon the voluntary system. Thus, after death from ether the vermicular movements of the intestine, although less active than normal, are very rarely, if ever, entirely absent.

Circulation.—The first effect of ether is usually to cause a pronounced rise in the arterial pressure, which is commonly maintained even through a prolonged ether narcosis, and may continue until manifest failure of respiration ; usually, however, it is after a time succeeded by a fall of pressure. According to Sansom,[13] the vessels of the frog's web are thrown into a persistent spasm by the inhalation of ether ; and in the research of Bowditch and Minot [14] upon mammals, the conclusion was reached that the vaso-motor centres are at first stimulated and afterwards depressed. Our present evidences show that there is, during ether anæsthesia, a rise of pressure, which is, at least in part, the result of increased cardiac action, but is probably also, in part, due to vaso-motor centric stimulation ; and that this rise is followed by a fall, the outcome of a simultaneous cardiac failure and vaso-motor centric and peripheral paralysis.

Blood.—It is frequently asserted that ether when added to blood coagulates it. A. Schmidt, however, states that the coagulation is due to ozone which has been generated in the ether, since freshly distilled ether does not coagulate albuminous substances.

The researches of Wittich [15] and of A. Schmidt [16] have shown that when ether is added to the blood of horses,* cats, or rats, the red corpuscles disappear in a very short time, and, as their stroma cannot be demon-

* Schmidt (*loc. cit.*, 23) says that sometimes crystallization fails in the blood of the horse.

strated by the aid of reagents, this disappearance is due to its solution. The oxyhæmoglobin thus set free is dissolved in the serum, but the presence of the ether soon causes it to crystallize. There is no proof that these changes occur to any extent when ether is inhaled; and the usual rapid recovery from the effects of the anæsthetic indicates that there is no profound alteration of the blood.

An imperfect study by Harley of the effect of ether on the gases contained in drawn blood indicates that ether does not exert much influence upon their proportional amounts. It is, however, quite possible that a more thorough investigation would give a different result.

SUMMARY.—Locally ether is a violent irritant. In excess it probably depresses all higher tissues, but it especially acts upon, first, the cerebrum, next upon the sensory, and then upon the motor side of the spinal cord. It usually produces death by asphyxia, due to depression of the respiratory centres. Its first action upon the circulation is that of a stimulant to the heart, and perhaps also to the vaso-motor centres. The large dose finally depresses both heart and blood-vessels.

THERAPEUTICS.—For a discussion of the use of ether as an anæsthetic, see page 106.

Administered by the mouth, ether has been used with advantage in various forms of *colic*, but is generally inferior to chloroform. When, however, as in cases of *retrocedent* or *internal gout*, there is with the painful gastric and intestinal spasm a condition bordering on collapse, the stimulant properties of ether make it very valuable.

In sudden *sinking-spells*, either from poison or from natural causes, ether, as a powerful and very quickly acting stimulant, is often indicated. In some cases of this description it may even be administered by inhalation. Of course, under these circumstances its influence should not be carried nearly to the point of producing anæsthesia.

As an *anthelmintic*, ether has been used with asserted success against the *tape-worm*. For this purpose, an ounce and a half have been administered at once, followed in two hours by a full dose of castor oil.

In *hysteria*, *neuralgia*, *nervous headache*, and *spasmodic neuroses*, such as *hiccough* and *asthma*, ether is occasionally employed with benefit.

When ether is swallowed, it produces a sense of strangulation and choking which seriously interferes with its use. For this reason, it is best given in capsules, or in ice-cold water. Probably large doses are best administered by putting them, mixed with an equal amount of brandy, on finely cracked ice before drinking. The dose is from one fluidrachm to half a fluidounce (4–15 C.c.).

Etherization by the rectum has been tried, but has been discarded on account of the severe irritation of the rectum and lower bowel which it causes, as well as because of the slowness of the production of insensibility.

CHLOROFORMUM—CHLOROFORM.

METHENYL CHLORIDE.

This substance, which was discovered in 1831 by Samuel Guthrie, of Sackett's Harbor, New York, is produced by the action of chlorine upon alcohol. It is a colorless, limpid, and neutral fluid, which is for practical purposes non-inflammable, although it can be made to burn with a greenish flame. Its taste is hot and sweetish, its odor fragrant and peculiar. It is soluble in alcohol and in ether, but when dropped into water it sinks, if pure, as transparent globules without milkiness. The alcoholic solution, when moderately diluted with water, forms an aromatic, sweetish liquid. It is antiseptic, and does not coagulate albumin.

The U. S. Pharmacopœia recognizes *Chloroform*, and requires that it should contain by weight 99 to 99.4 per cent. of absolute chloroform and 0.6 to 1 per cent. of alcohol.

PHYSIOLOGICAL ACTION.—*Local Effects.*—Although somewhat of an anæsthetic, chloroform applied locally is a powerful irritant. On the skin it produces redness and burning; if the evaporation be restrained, vesication will be induced by it. Taken into the mouth, it causes a burning sensation, and, when swallowed, a sense of warmth in the stomach.

Absorption and Elimination.—Chloroform is rapidly absorbed through the mucous membrane of the respiratory and digestive apparatus. Its exact fate in the body is at present unknown. It is certainly eliminated, at least in part, unchanged in the expired air after administration by the mouth (Benedicenti[1]); and after its inhalation has been detected by Fubini and by Siolfatti,[2] in the urine. It is probably, however, in part decomposed in the system, since A. Zeller[3] has found that the chlorides of the urine are nearly doubled by its inhalation.

The vapor of chloroform, when inhaled, produces symptoms seemingly similar to those induced by ether, except that the choking sensations are absent, and that the stage of excitement is generally, but not always, shorter and less violent than is that of etherization.

General Action.—The division of chloroform-narcosis into three stages was first proposed by Sabarth,[4] and, though somewhat arbitrary, is practically useful. In the first of these the symptoms are similar to those of alcoholic intoxication. This stage is generally very short, but in athletic persons, and especially in those who have been intemperate, it may be very long and very violent, and may persist after loss of consciousness. In drunkards, this excitement at times cannot be overcome without grave danger to life. During this first stage, although consciousness is not lost, the sensibility is generally blunted, but very rarely is it altogether annulled. Coleman (Sansom, *Chloroform*, 55, Philadelphia, 1866) states, however, that he has extracted his own teeth without pain; and Snow relates the anecdote of a child who played with his toys during the operation of lithotomy.

During the second stage, which is that of anæsthesia, the conscious-

ness and sensibility are abolished, the muscles are relaxed, and the patient lies perfectly quiet. This is the surgical stage, during which ordinary operations are performed. As already intimated, in some cases the first and second stages are united, so that violent excitement, muscular spasm, and rigidity may coexist with loss of consciousness and of sensibility.

The third stage is one of profound narcosis, with stertorous breathing, intense muscular relaxation, abolition of the ordinary reflexes, and fall of bodily temperature.* This is always a condition of danger, and its induction by chloroform, except under very peculiar circumstances, is unjustifiable.

The pulse in the first stage of chloroform-narcosis may be quickened, even apparently strengthened; in the second stage it is generally about normal in frequency, but is more or less weakened; in the third stage it is rapid and weak. Noel[5] calls attention to a cervical venous pulse, most marked in the external jugulars, which he asserts frequently occurs during the waking up from chloroformization. He believes it to be a symptom of serious cardiac embarrassment. E. Simonin[6] found that the temperature usually rises during the first stage (0.1°–0.9° C.), falls slightly during the second or remains above normal, and falls decidedly during the third stage.†

The experiments of Holmgren, Kratschmer, H. C. Wood, Jr.,[7] and others have demonstrated that the action of chloroform upon the nervous system is entirely parallel to that of ether (see page 93), the difference being simply one of intensity of power. In practical anæsthesia the stage of excitement is usually much less severe with chloroform than with ether, but, according to H. C. Wood, Jr., this hyperexcitation depends upon the ether vapor being given to man habitually in concentrated form, when the anæsthesia is induced slowly by air containing a very small percentage of the anæsthetics, the stage of excitement being greater with chloroform than with ether. The motor disturbances seen early in chloroformization, as in etherization, have been supposed to indicate a condition of spinal

* Baudin (*Le Progrès Méd.*, Sept. 1874) called attention to the pupil as a guide in chloroformization, stating that, although at first it is uniformly dilated, afterwards it is uniformly immovably contracted, and that this is the period for operating. Schläger is in accord with Baudin; in one hundred and twenty out of one hundred and twenty-two cases observed, the pupil was dilated during the stage of excitement, and during complete anæsthesia narrowly contracted. He also states that if during anæsthesia the pupil return to normal, more chloroform is required, but if it suddenly dilate, danger is imminent. At present, however, the condition of the pupil cannot be considered a safe guide in anæsthetization. Dogiel (*Reichert's Archiv für Anat.*, 1866) affirms that in rabbits, during the stage of excitement, the pupil is contracted, during anæsthesia dilated. Schiff has strenuously combated the conclusions of Baudin; and in a very careful series of experiments on animals W. H. Winslow found that the state of the pupil varies greatly in the same stage of anæsthesia. Thus, in complete anæsthesia, sometimes the pupil was widely dilated, sometimes contracted; and death sometimes occurred with a dilated, sometimes with a contracted, pupil,—in the former case probably being syncopal, in the latter asphyxial (*Phila. Med. Times*, vi. 275).

† As the result of chemical studies, Julius Pohl (*Arch. f. Exp. Pathol. u. Pharm.*, 1891, xxviii.) believes that more chloroform exists during the narcotic period in the brain-tissue than in the blood coming to it.

stimulation, but have been shown by Bert[8] to be of purely psychical origin.

Bernstein[9] found that there was no perceptible difference in the conducting power of the two ischiatic nerves of a frog chloroformed after one of its iliac arteries had been tied.

Circulation.—In some animals the first effect of the inhalation of chloroform upon the circulation is a decrease in the frequency of the heart's action. Dogiel believes that this is due to a stimulation of the inhibitory centres, because he has found that it does not occur after section of the vagi. The after-increase in the rapidity of the pulse appears to be due, at least in part, to paralysis of the inhibitory centres, upon which chloroform seems to act as upon the oculo-motor centres, producing in them at first excessive functional activity, but afterwards functional paralysis. Both Kratschmer and Knoll (see page 92) have noticed in rabbits, when either ether or chloroform is inhaled through the nose, a momentary rise of arterial pressure corresponding to an arrest of respiration, and, like it, evidently produced by irritation of the peripheral trigeminal branches.

As was first proved by the English Chloroform Committee,[10] after the first half-minute of the inhalation of chloroform there is a progressive lowering of the arterial pressure. This has been confirmed by all observers and is an established fact. The matter still somewhat in dispute is as to the immediate mechanism of the fall. Sansom and Harley state that there is a spasm of the small vessels, which can be readily seen to occur in the web of the frog during chloroformization. Not until the third stage is reached, according to these authors, do the vessels relax into dilatation. If these observations be correct, chloroform first stimulates and afterwards depresses the vaso-motor centres. In accordance with this are the important experiments of Gaskell and Shore,[11] who find that the local application of chloroform to the medulla or its injection into the cerebral artery produces an immediate rise of blood-pressure, usually accompanied by a slowing of the heart, which is followed by a fall of pressure so soon as the chloroform is able to diffuse itself throughout the circulation. Gaskell and Shore further so connected the carotid arteries and jugular vein of an animal (A) with the similar vessels of a second animal (B) that the brain of A was fed exclusively with blood from B. It is plain that chloroform given to B would reach the brain of A but would not reach the heart of A. Under these circumstances it was found that chloroform administered to B produces rise of blood-pressure in A. In a second series of experiments the blood-vessels of A were so connected with those of B that when chloroform was administered to B it reached the heart of A and all other portions of the body except the brain. When this was the case, chloroform given to B produced an immediate fall of pressure in A without there having been any rise. In other words, when chloroform reached the vaso-motor centres and not the heart, it caused rise of arterial pressure ; when it reached the heart and not the vaso-motor centres, it caused fall of pressure.

The only experiments with which we are acquainted, to which any weight should be attached, as indicating that chloroform primarily paralyzes the vaso-motor centres, are those published as long ago as 1874 by H. P. Bowditch and C. S. Minot.[12] In these experiments, which were made upon curarized animals, "irritation of the saphena nerve caused a much less marked rise of blood-tension than when the anæsthetic was not used. Sometimes there was absolutely no rise of tension to be observed, while at other times the rise was from one-third to one-half that produced by the same irritation on an animal not subjected to the action of chloroform." Further compression of the carotid in the chloroformed animal did not cause the customary spasm and rise of arterial pressure.

It must be remembered that these experiments of Bowditch and Minot were made at a time when the importance of the subject had not been fully realized ; that on the carotid but a single experiment was made ; and that there was frequently in the experiments of Bowditch and Minot a great rise of pressure following irritation of the sensitive nerve, though the rise was not as great as in the normal dog.

It must also be remembered that chloroformization interferes with the functional activity of the sensory side of the nervous system, so that an impulse produced by irritation of the sensitive nerve fails to reach the vaso-motor centres in full force. In many of the experiments of Bowditch and Minot, irritation of the saphenous nerve produced distinct rise of pressure, showing that the vaso-motor centre was not paralyzed, though the arterial pressure had fallen very distinctly : late in chloroform-poisoning there is a vaso-motor paralysis, and it may very well be that in the single carotid experiment of Bowditch and Minot the chloroformization had been carried on to the fullest extent. The results, therefore, of Bowditch and Minot are not proof of the incorrectness of the theory of Gaskell and Shore ; and the drift of the present evidence is to show that chloroform in the *earliest stages of its action stimulates rather than depresses the vaso-motor centres.*

On the heart itself chloroform undoubtedly exerts a steady, powerful depressing influence. Injected into the jugular vein,* it instantly arrests the heart's action and destroys its muscular irritability † Even the vapor of chloroform, when locally applied to the exposed heart, paralyzes it.[13] When artificial respiration is maintained, the effect of chloroform is very apparent.[14] By a very ingenious series of experiments, MacWilliam[15] has proved that very early in chloroform anæsthesia there is a marked diminution of the force of the auricular and the ventricular beats, accompanied by dilatation of the cardiac chambers, due to the direct influence of the chloroform. Again, as stated by Gaskell and Shore, even the tracings of the Hyderabad Commission demonstrate that from the very beginning of chloroformization the excursions of the heart-beat, as shown

* See also MacWilliam's experiments.

† Glover (*Edinb. Med. Journ.*, 1842), Gosselin (*Arch. Gén.*, 1848), Anstie, and H. C. Wood.

on the Fick manometer in the most typical manner, get smaller and smaller as the pressure falls. Indeed, as Gaskell and Shore say, "every one would agree with the Commission that they [the pulse-waves] are of the typical kind which would be produced if direct weakening of the heart were the cause of the fall of blood-pressure in chloroform administration."*

Putting all the evidence together, it seems to us to have been completely demonstrated by physiologists, first, that chloroform is a *direct depressant and paralyzant to the heart-muscle or its contained ganglia*;† second, that the *fall of blood-pressure which occurs in chloroformization is in great part due to this direct depression of the heart.*

Respiration.—So soon as psychical excitement has passed off, or, at first, if there be no such excitement, the respirations may be rendered slower by chloroform, but after a time they are generally quickened, and as the inhalation is persisted in they become more and more shallow, irregular, and distant, and finally cease. In 1870 Paul Bert[16] asserted that during chloroformization there is more than the normal percentage of oxygen in the blood, but in 1885 he affirmed that there was less than the normal percentage.[17] There does not seem to be much doubt that the results of L. G. de Saint-Martin[18] are correct,—namely, that whilst (probably on account of excessive respiration from excitement) in the beginning of chloroformization there is sometimes hyperoxygenation of the blood, the rule during full anæsthesia is decrease of the oxygen of the blood with increase of the carbonic acid.

Blood.—According to Harley,[19] blood to which as little as five per cent. of chloroform has been added becomes very liquid and of a bright arterial hue. After a time crystals of oxyhæmoglobin form in it. Boett-

* The work of the Hyderabad Commission has become so celebrated that it hardly seems necessary to explain that they reached with extreme positiveness the conclusion that chloroform kills purely through the respiration, and that it is a perfectly safe anæsthetic. Rather strangely, they based their belief that the fall of blood-pressure under chloroform is not due to weakening of the heart chiefly upon certain atypical tracings which they obtained. The publication of these tracings shows, in the language of Gaskell and Shore, "that these cases afford no proof whatever that the heart's action is not impaired by the action of chloroform."

† REFLEX CARDIAC INHIBITION.—Intense irritation of the respiratory passages may have a very marked influence upon the heart by acting reflexly through the inhibitory centres, and some authorities believe that sudden arrest of the heart's action in this way occasionally occurs during chloroformization. Vulpian has shown (see CHLORAL) that a heart under the influence of chloral, a substance closely allied to chloroform in its heart action, is exceedingly sensitive to slight inhibitory impulses. It is notorious that during chloroformization death has often occurred immediately after the first incision. This suggests that the fatal syncope may be due to the irritation produced by the knife, and that it is wiser for the surgeon to wait until complete chloroformization occurs with absolute abolition of reflexes. We are, however, not inclined to attach much credence to the theory of reflex inhibitory arrest of the heart. In a careful series of experiments (see address on *Anæsthesia*) H. C. Wood found it easy in the dog to cause marked reflex inhibition of the heart by irritating the upper air-passages with chloroform, but it was impossible to produce complete cardiac arrest. The mere rapidity of the occurrence of the syncope after the first whiff of the chloroform is of little importance as an argument in favor of the theory that death is caused by irritation of the peripheral nerves in the lungs, since the pulmonic absorption of chloroform is practically instantaneous and the blood goes directly from the lungs to the heart.

cher[20] was, we believe, the first to study these changes closely. The first alteration noticeable in the red blood-disks is a diminution of their size, which A. Schmidt and F. Schweiger-Seidel[21] assert to be due to contraction, because when blood is treated with water until the red globules disappear, and carbonic acid gas is passed through the liquid until they reappear, on the addition of chloroform the sharply contoured bodies will be seen to undergo marked contraction. As was first shown by Boettcher and confirmed by Schmidt and Schweiger-Seidel, chloroform alone produces no other alteration than contraction in the red blood-disks. If, however, air be admitted to blood containing chloroform, the corpuscles rapidly disappear, dissolving in the serum, out of which, after a time, oxyhæmoglobin crystallizes. Both of the authorities quoted believe that the latter changes are due to oxidation. Boettcher states that chloroform-vapor mixed with air converts enough of the oxygen of the latter into ozone to react with iodinized starch-paper ; and Schmidt and Schweiger-Seidel have found that an excess of carbonic acid in the blood interferes with the changes caused by chloroform. From these facts it seems probable that their opinion as to the nature of the blood-changes is correct. Harley has studied the effect of chloroform on the absorption of gases in the blood. He states that when chloroform is added to fresh blood, and the mixture allowed to stand for twenty-four hours, a marked increase takes place in the proportion of oxygen and a lessening in that of carbonic acid. This is in accord with the theory just mentioned ; for, after the complete oxidation of the hæmoglobin brought about by the chloroform, further consumption of oxygen could not occur, and, as it continued to be absorbed from the air, it must accumulate instead of being converted into carbonic acid.

After death during chloroform anæsthesia the presence of gas has been frequently noticed in the blood-vessels and in the heart. Contrary to the conclusions reached by various authors, Kappeler[22] has shown that usually, if not always, the gas has been liberated by putrefactive changes occurring after death. The statement of Pirogoff, that he has witnessed the throwing out of gas from the blood during life, has never been confirmed, but it is possible that the chloroform may have some influence upon the capacity of the blood for holding gases.

How far, during ordinary narcosis, chloroform produces changes in the blood is uncertain. A very sensitive test of the destruction of the red disks in the body is found in the production of icterus ; icterus following chloroformization is very rare, but the assertion of Frerichs that it does occur is correct.* Bernstein[23] and Leyden[24] have found traces of bile-pigment in the human urine after chloroform-narcosis ; whilst Nothnagel[25] detected bile coloring-matter in the urine of rabbits after subcutaneous injection of chloroform or ether. Husemann[26] intimates, on what authority we do not know, that after anæsthesia bile-acids (the precursors of

* Brainerd, *University Med. Magazine*, 1899.

icterus) appear in the urine ; but Kappeler,[27] in twenty-five cases of chloroform-narcosis, was not able to obtain a trace of biliary coloring-matter. Sokolovski[28] asserts that the first few hours after chloroformization there is a decrease of the immature white blood-corpuscles, with an increase of the mature white blood-corpuscles, followed by gradual return to normal.

General Nutrition.—That chloroform affects the general nutrition of the body is demonstrated by the wide-spread fatty degeneration which sometimes follows long-continued narcosis produced by it (see page 117), as well as by the observations of Strassmann,[29] who found that a pronounced increase of the nitrogenous elimination follows chloroform-narcosis, an increase which would seem to be directly due to the anæsthetic, since Salkowski demonstrated that chloroform-water given to dogs distinctly increases the destruction of nitrogenous substances in the body without producing narcosis.*

According to the researches of Strassmann[30] and of Salkowski,[31] chloroform is an active antiseptic and germicide. Both Salkowski and A. Bertels[32] find that the drug also checks the action of pepsin and other unformed ferments.

THERAPEUTICS.—For a discussion of the use of chloroform as an anæsthetic, see page 106.

When administered by the mouth in sufficient quantity, chloroform produces symptoms similar to, but much more permanent than, those which it causes when inhaled. It is, however, very rarely, if ever, used in this way for its constitutional effect, but is sometimes of advantage in severe *neuralgia*. When quinine for any reason cannot be administered in an *ague*, a sufficient dose of chloroform (ʒss to ʒi) to produce a mild narcosis, just before the expected time for the recurrence of the chill, will usually abort it.

Chloroform by the mouth has been also highly recommended as a vermifuge in cases of *tape-worm*, but is of very doubtful value.

When chloroform is taken into the stomach, a considerable portion of it is, without doubt, evaporated, so that the intestinal canal becomes filled with the vapor. Chloroform, therefore, when so placed exerts both a local anodyne and a stimulant carminative action. For this reason it is extremely valuable in all cases of *colic*, and it will often even assuage the pain of *colica pictonum*.

Externally, as a rubefacient and anodyne, chloroform is very largely combined with other substances into liniments, which are especially useful in cases of *chronic neuralgic* or *rheumatic pains*.

Poisoning has been produced by the swallowing of chloroform. The symptoms induced have been stupor, with contracted, or, in later stages, dilated, pupils, and a stertorous respiration, which finally becomes very

* J. Petruschky (*Deutsche Med. Wochensch.*, 1891, xvii.) has noticed that after death from chloroform the intercellular juices become rapidly acid, and he has found that this is not peculiar to chloroform, but takes place also after death from ether, arsenic, and other poisons.

irregular, shallow, and often distant. The amount necessary to destroy life probably varies greatly, but, according to L. Lewin, a single drachm has produced death. In some cases[36] the fatal result has occurred from secondary gastritis many days after taking the medicine ; and not rarely violent gastritis with jaundice apparently from inflammation of the gall-ducts has been produced. Recovery has occurred after the ingestion of three ounces without vomiting ;[33] also five ounces. The treatment consists in the use of the stomach-pump and of the various ordinary methods of arousing a narcotized patient, especially the alternate cold and hot douche, artificial respiration, and the very cautious use of diffusible stimuli if required. Death may occur during the narcosis, or the patient may survive this and perish from inflammation of the trachea, œsophagus, and stomach, caused by the local action of the chloroform.

The recognition of chloroform as the probable cause of any given death cannot be based upon the post-mortem appearances. Indeed, the latter are of no value in deciding such a question. The anæsthetic may, however, be recovered by distillation of the lungs and blood within a certain period of time after death. As to the length of this time, so far as we are aware, no investigations have been made.

Criminal Relations.—Experiments made at the Philadelphia Hospital and confirmed by Dolbeau[34] have proved that persons sound asleep may be chloroformed without being awakened. Anæsthesia cannot, however, be produced in any one partially awake, or even sleeping lightly, without his or her knowledge.

Quite a number of professional men have been accused, and some convicted on the charge, of committing rape on females in whom they had induced anæsthesia. No doubt the women believed that they had been violated ; but it is certain that in many of the cases, and probable that in all of them, they mistook for the real act the subjective erotic sensations induced by the chloroform or ether. The valuelessness of the testimony of persons as to occurrences during the time of their intoxication with anæsthetics should be recognized by law as a governing principle of evidence.

ADMINISTRATION.—Internally, from fifteen drops to a fluidrachm (0.9–3.7 C.c.) of chloroform may be given in emulsion, or, as it has been stated, dissolved in glycerin (one to three). The deep injection of half a drachm of chloroform has been recommended very strenuously by Bartholow in obstinate *neuralgia*, and has found some favor in France.[35] In the only case in which we have tried it, one of trigeminal neuralgia, the local symptoms caused by it were so severe as to imperil the life of the patient. The U. S. Pharmacopœia recognizes a spirit) SPIRITUS CHLOROFORMI—six per cent., U. S.), dose, one to two fluidrachms (3.7–7.5 C.c.), and an emulsion (EMULSUM CHLOROFORMI—four per cent., U.S.); also a liniment (LINIMENTUM CHLOROFORMI—thirty per cent., U.S.).

ETHYL BROMIDE is a colorless, very volatile, very fluid liquid, having the specific gravity 1.49, of a sweet, chloroform-like smell ; not

readily inflammable ; insoluble in water, but mixing with ether, chloroform, fat, and ethereal oils in all proportions. It does not solidify at 32° F. Any preparation of it which has color, or seems irritating, or has a disagreeable smell, is unfit for medicinal use. It must clearly be separated by the practitioner from *ethylene bromide*, which has a specific gravity 2.16, and solidifies at 32° F. into a crystalline mass. At least one, and probably more deaths have been produced by the substitution of the ethylene bromide for the ethyl bromide.[1] Ethyl bromide degenerates under the influence of light and air, and should, therefore, always be kept in small bottles of dark glass, closely corked.

Ethyl bromide was first proposed as an anæsthetic by Thomas Nunnelly in 1849, but was not brought earnestly before the profession until 1876–77, when attention was directed to it by Rabuteau in France and Laurence Turnbull in the United States. Its influence is usually manifested in a few seconds after the beginning of an inhalation, and lasts from one and a half to three minutes after the removal of the drug from the mouth. A peculiarity that has been noted by several observers is a tendency for sensibility to be lost before consciousness, and Montgomery has especially noted that during parturition ethyl bromide will do away with most of the suffering without arresting the pains or producing complete relaxation of the muscles ; indeed, it appears to be common for the general muscular tonus to be greatly increased by it. According to John H. Brinton, muscular excitement, as shown by rigidity, local spasms, and even general tetanus with opisthotonos, occurs so frequently as seriously to interfere with the anæsthetic use of the drug, especially as this condition during a surgical operation is attended by great increase of hemorrhage.[2] During narcosis the corneal and pupillary reflexes are usually preserved, and the eyes are sometimes wide open and crossed from contractions of their muscles (Gilles[3]).

The physiological action of ethyl bromide has been partially studied by Schneider, by Abonyi, by Thornton and Maxwell,[4] and by H. C. Wood. Schneider states that the arterial pressure does not fall until very late in the bromide narcosis, and that death takes place always through arrest of the respiration. In these statements he is in accord with results obtained by Abonyi,[5] who was not able to detect any alteration in the beat of the exposed heart of the frog in which narcosis was produced. On the other hand, the experiments of Thornton and Maxwell are in agreement with our own in showing that fall of the arterial pressure occurs very early and increases steadily with a persistent inhalation. In H. C. Wood's experiments ethyl bromide seemed to act on the circulation precisely as does chloroform, although less powerfully. It is possible that this difference of result has depended upon some of the ethyl bromide used being impure.

In the eighth edition of this book it was stated that "clinical results show that ethyl bromide is a very dangerous anæsthetic," there at that time having been three deaths reported as produced by it in a very

limited number of administrations.[6] Gilles, however, asserts that in twenty thousand successive administrations of ethyl bromide in Germany there has been no fatal result when a chemically pure bromide has been administered. Nevertheless, the deaths recorded by A. Gleich[7] and by Suarez de Mendoza[8] show that the pure bromide is capable of causing a fatal accident, since in Gleich's case the bromide given was that habitually used in the large German clinics, and in Mendoza's case chemical analysis after death proved the purity of the drug. When a very brief anæsthetic effect is desired ethyl bromide may be used as probably no more dangerous than chloroform ; but the fugaciousness of its action and the muscular excitement which it causes forbid its general employment in major surgery, whilst the recent developments of local anæsthesia greatly lessen the field of its utility in minor operations. The ease with which ethyl bromide undergoes change offers a serious difficulty to its use. Certainly the surgeon should see that the individual specimen employed has every appearance of being pure.

Hennicke has proved that ethyl bromide undergoes decomposition in the system with the liberation of bromine compounds, and as bromine is much more poisonous than chlorine, it is to be, *a priori*, expected that ethyl bromide will be more apt to produce wide-spread organic changes in the general tissues than is the older anæsthetic. In accordance with this, cases have been reported by Reich[9] and by Flatten,[10] in which the inhalation of the bromide has been followed by persistent vomiting, general weakness, and death (in from one to seven days), and in which the liver, the kidneys, and the heart-muscles were found to have undergone acute fatty degeneration.

PENTAL—TRIMETHYLETHYLENE.—This is a colorless, highly inflammable liquid, boiling at 100° F., originally proposed by W. Lombardino as a practical anæsthetic. It acts with great promptness without marked disagreeable symptoms, producing a short narcosis, which is, however, longer than that caused by ethyl bromide. In three hundred narcoses by it, P. Philipp[1] failed to find any depression of the heart or severe asphyxia. Pental is also commended by Kleindienst, who, however, noted that very frequently three or four days after the narcosis there was abundant albuminuria, and not rarely hæmaturia or hæmoglobinuria occurs. In a study of the drug by David Cerna,[2] anæsthesia caused by it in the dog was found to be accompanied always by marked fall of the arterial pressure, and the conclusion was reached that the remedy depresses the heart. The alleged action of pental upon the kidneys, if it be true, negatives its use as a practical anæsthetic. From the statistics of Gurlt,[3] it is the most dangerous of all the anæsthetics, there having been three deaths in the six hundred reported narcoses.

METHYLENE BICHLORIDE was introduced to the notice of the profession by B. W. Richardson,[1] as an anæsthetic similar to, but more pleasant

and possibly safer than, chloroform, and has been rather extensively used in London. It has never been largely employed in this country. There is no way of knowing how many times it has been administered, but nine cases of death from its use are recorded.[2] The detailed phenomena in these cases indicate that, like chloroform, methylene bichloride kills by paralyzing the heart. It is not probable that it will ever come into general use as an anæsthetic.

PRACTICAL ANÆSTHESIA.—Although various substances have from time to time been used as anæsthetics, the surgical profession has practically settled down to the employment of either ether or chloroform, and experience seems to show that there are no other known agents which act as well as do these two liquids. The question as to which of them should be preferred is a vital one, as are also the questions how to recognize and how to treat the accidents which occur during anæsthesia. It must be in the beginning granted that the production of anæsthesia is always attended by a danger which, though small, is positive, and that fatal accidents will always occur from time to time. There are few things in medical literature more tiresome than the arrogant assertions of various surgeons that they have never had a fatal accident from chloroform or ether because of the special methods by which they have used them. May their conceit die with them. All that a surgeon can hope for is to reduce the number of these accidents to a minimum.

In selecting the agent, convenience of administration both to the surgeon and to the patient is, of course, of importance; but we hold that such advantage ought not to be pitted against danger of fatal results. For reasons which were given in H. C. Wood's address before the Berlin International Congress, it is doubtful whether half the deaths produced by anæsthetics are reported, but thousands have been recorded. The ratio of deaths to inhalations for chloroform is given by Lyman as 1 in 5860; by Richardson as 1 in 2500 to 3000 (see also Coats,[1]); whilst Andrews records it for ether as 1 in 23,204, and Lyman as 1 in 16,542. In nearly one million of inhalations (George M. Gould[2]), the mortality was, with chloroform, 1 in 3749; ether, 1 in 16,675. Garree[3] gives the deaths in three hundred and fifty thousand cases of recent inhalation of ether as 1 in 14,000. Gurlt[4] in over three hundred and thirty thousand cases gets the mortality for chloroform as 1 in 2075; ether, 1 in 5112; chloroform and ether mixed, 1 in 7613; A. C. E., 1 in 3370; ethyl bromide, 1 in 5396.* These statistics are, taken together, so enormous

* Although not able to give definite statistics upon the fact, we are strongly inclined to believe that deaths from anæsthesia, and especially from ether, are proportionately more frequent in Europe than in America. If this be so, one reason, it seems to us, is to be looked for in the use of the Clover and other forms of closed inhalers, with which the anæsthesia produced is to a greater or less extent due to mechanical asphyxiation. Some years since a method of rapid etherization, in which the ether was put into a gallon jar and the patient forced to breathe in and out of the jar, was tried by Agnew in the University Hospital. Anæsthesia was produced almost at once with very little excite-

in extent and so concordant that it must be considered established that the ratio of deaths from chloroform is about four times greater than that from ether.

The assertion that the inhalation of chloroform is less dangerous in tropical than in temperate climates has been made so frequently and so earnestly by various surgeons practising in hot countries, and is seemingly so sustained by statistics, that it is probably correct. It has received a curious confirmation from a study of reported deaths from chloroform by Thomas R. Evans,[5] which appears to show that most of these deaths have occurred during the cold seasons of the year. It is entirely possible that the increased volatility of chloroform at high temperature facilitates its elimination from the body and thereby lessens the dangers of its use.

The advantages of chloroform over ether are—that it is less disagreeable to the patient, produces less excitement, more speedily reduces the subject to insensibility, and is less apt to cause excessive after-nausea and vomiting. These advantages do not at all counterbalance the great danger to life, and we believe that the surgeon is not justified in using chloroform unless under certain circumstances, and for certain definite reasons.

Moreover, we believe that many of the so-called disadvantages of ether can be overcome by a little care. If the stomach be empty, the after-nausea will rarely be severe, and when the ether is properly given with an Allis inhaler, the average time required for the production of complete insensibility is eight minutes, and the sense of suffocation and the symptoms of excitement are rarely pronounced.

A study of the reasons of the great fatality of chloroformization leads to a study of the methods by which chloroform and ether produce death. The teaching of H. C. Wood was formerly in accordance with the general professional belief: "First, that although ether in moderate doses acts as a stimulant to the circulation, yet, in overwhelming amount, it is capable of depressing the heart, but that such depression of the heart is always less than the depression of the respiration; secondly, that chloroform may produce death by paralysis of the respiratory centre, or by a simultaneous arrest of respiration and circulation, but that primary paralysis of the heart may occur, and is especially prone to do so when the chloroform vapor has been given in concentrated form."

These teachings have been very strongly combated by the so-called Hyderabad Commission, led by Lauder Brunton, of London, who, as the result of four hundred and fifty experiments made upon the pariah dogs of India, came to the absolute conclusion that chloroform never kills by causing sudden stoppage of the heart. There is no space in the present volume to go over in detail the evidences which were brought forward by H. C. Wood in his Berlin address. It was, however, we think,

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ment, but in a very brief period the Clinic nearly lost two patients from anæsthesia, and the method fell at once into desuetude. It was really a plan of asphyxiation rather than of etherization.

definitely proved that the clinical and experimental facts are accordant, and "that chloroform acts much more promptly and much more powerfully than does ether, both upon the respiratory centres and the heart; that the action of chloroform is much more persistent and permanent than is that of ether; that chloroform is capable of causing death either by primarily arresting the respiration or by primarily stopping the heart, but that commonly both respiratory and cardiac functions are abolished at or about the same time; that ether usually acts very much more powerfully upon the respiration than upon the circulation, but that occasionally, and especially when the heart is feeble, ether is capable of acting as a cardiac paralyzant and may produce death by cardiac arrest at a time when the respirations are fully maintained." These conclusions, which were based upon a thorough examination of clinical records and a very large number of experiments performed in the laboratory, have since been confirmed by John A. MacWilliam,[6] who has recorded cases of death in the lower animals from chloroform, in which there was primary collapse of the heart; and by the studies of the Lancet Commission,[7] which found that out of three hundred and fifty-seven deaths caused by chloroform, whose records it had examined, the fatal result was caused by cardiac failure two hundred and twenty-seven times, by respiratory failure eighty times, and by simultaneous failure of the two functions seventy-seven times.*

MacWilliam also found that in the dog cardiac weakness and dilatation are always caused by chloroform, and in rare instances are produced by ether. Both chloroform and ether are capable of causing arrest of the heart by a direct action upon the viscus, but chloroform is more apt to cause fatal accidents than ether, partly because its influence upon the heart is very much more decided, and partly because it persists much more tenaciously than does ether in its action upon the whole organization after its administration has been interrupted. It lets go its hold much less easily and much less rapidly than does ether.†

Alexander Wilson believes that the "cardiac failure" of chloroformization is chiefly a vaso-motor paralysis. Undoubtedly vaso-motor paralysis plays a part in the production of the untoward results, but we see no sufficient reason for supposing that it is the chief factor.

Another fact worthy of notice is the question whether the lowered blood-pressure itself has any effect upon the respiration. In a research published by H. C. Wood and W. S. Carter,[8] it was proved that lowered arterial pressure has only a comparatively feeble effect upon the respiration, although a great fall of pressure does depress the respiratory function. Evidently prolonged failure of respiration tends to depress the

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* See also cases reported by Alexander Wilson, *London Lancet*, Sept. 11, 1897.

† A possible explanation of the peculiar tenacity is that chloroform is stored in the nerve-centres, outside of the blood-vessels. Julius Pohl (*Arch. f. Exp. Pathol. u. Pharm.*, 1891, xxviii.) affirms that his analyses have proved that more chloroform exists during the narcosis in the brain-tissues than in the blood coming to it.

circulation, and prolonged failure of circulation tends to depress the respiration. The two functions are thus far interrelated.*

On account of its being less dangerous, ether should always be selected as the anæsthetic agent in general surgery unless definite reasons exist for the preference of chloroform. These reasons may be epitomized as follows. First, when, as in the case of war, circumstances make it practically impossible to obtain the bulkier anæsthetic. Second, when the symptoms themselves are of such character as immediately to threaten life, especially if at the same time there be, as in a tetanic convulsion, some existing condition which greatly interferes with the entrance of the anæsthetic into the lungs. Third, the existence of certain contra-indicating bodily conditions hardly to be spoken of as disease. How cogent the reasons under the present heading are to be considered we are uncertain, but F. W. Hewitt affirms that in old people with very rigid chests etherization is often attended by great difficulty and chloroform is well borne, and also cites extreme obesity as a bodily state in which ether is not well borne, and in which chloroform or a mixture of ether and chloroform is preferable. Fourth, existence of certain diseases which, to a greater or less extent, not only contra-indicate the use of an anæsthetic, but also, when the anæsthetic must be used, modify the choice of the agent by the surgeon. The existence of a contra-indicating disease does not forbid the use of an anæsthetic. If a major surgical operation be imperatively demanded, and if it be impossible by the use of local anæsthetics to prevent the pain and emotional excitement which would attend the operation in a perfectly conscious sensitive patient, the surgeon must decide whether the needs of the case overbalance the added risk to the operative procedure. The contra-indicating diseases are of such importance as to demand here extended consideration. They are : Organic Brain Diseases, including Tumors ; Atheromatous Conditions of the Blood-Vessels ; Organic Affections of the Heart, of the Lungs, and of the Kidneys.

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* *Mixed Anæsthetics.*—A number of combinations of one or more anæsthetics have been to a greater or less extent used by surgeons with the hope of overcoming or avoiding the deleterious effects of the one ingredient by the action of another. The most used of these is the so-called *A. C. E. mixture*, composed of one part of alcohol, by weight, two parts of chloroform, and three parts of ether. The latest is *Schleich's mixture*, in which the attempt is made to have an anæsthetic the boiling point of which shall approximate to the bodily temperature, and for this purpose benzine is used as a diluent. The proportions of Schleich's mixture are three parts chloroform, ten parts ether, one part benzine. The difficulty with all these combinations is that their ingredients are not chemically combined but simply mixed together, and therefore obey each the law of its own volatility; so that the surgeon can never be certain of knowing exactly what the patient is inhaling at any time; the only certainty being that the original mixture is not being taken into the lungs. In regard to Schleich's mixture, H. C. Wood, Jr. (*Phila. Med. Journ.*, April, 1899), has demonstrated that the benzine is not, as affirmed by Schleich, a "nearly inert" diluent; on the contrary, it is, although almost devoid of anæsthetic properties, a powerful depressant of the respiratory centres and also of the heart and probably of the vaso-motor system. It is evident that Schleich's mixture is distinctly inferior either to ether or chloroform used alone. If the surgeon is intent on having what may be termed a "mixed anæsthesia," it would seem better to put ether upon the inhaler or sponge, and then a few drops of chloroform.

Brain.—Brain-tumors and other organic forms of cerebral disease are very serious contra-indications to the use of anæsthetics ; even when there is no demonstrable brain-lesion, if there be reason strongly to suspect atheroma of the vessels, anæsthesia should be induced with the greatest reluctance. In a number of cases apoplexy has resulted during or immediately after the anæsthesia. The fatality of anæsthesia when there is organic brain disease appears to be due to the loss of resisting power in the respiratory centres, death usually occurring through failure of respiration. We know of no sufficient data to enable us to decide which, in these cases, is the safer agent, chloroform or ether, but the greater power and persistency of chloroform would seem to make it especially dangerous. The danger of apoplexy is much greater under nitrous oxide than under ether, and probably under ether than under chloroform.

Disease of the Heart.—When valvular disease of the heart does not produce any distinct functional disarrangement of the heart, and when the heart-muscle is in a fair condition of health, anæsthesia may be induced, provided the circumstances of the case are such as to justify the surgeon taking a slightly increased risk. The key to the situation is not the valvular lesion, but the condition of the muscle. A loud murmur usually depends for its loudness not only upon the character of the valvular lesion but also upon the force which drives the blood through the diseased orifice. A loud murmur is, therefore, on the whole, not more strongly contra-indicative of anæsthesia than is a feeble one ; indeed, as the feeble murmur is more commonly associated with feeble walls, greater care must be exercised when such murmur exists than when a loud bruit everywhere forces itself upon the physician's attention. In all cases of heart disease, whenever it is possible to avoid the use of an anæsthetic by the employment of cocaine or by other local device this should be done. No condition of the heart is, however, an absolute contra-indication to the use of the anæsthetic ; under certain circumstances anæsthesia may be produced when the heart is in advanced fatty degeneration. It must be remembered that the shock and nerve-strain which attend a major surgical operation without anæsthesia would endanger the arrest of a fatty heart even to a greater degree than would the anæsthesia, so that the question is, after all, as to the imperativeness of the proposed operation.

In diseases of the heart ether is usually preferable to chloroform ; indeed, when the heart is very feeble or the cardiac muscle is degenerated, the action of chloroform upon the heart makes it very dangerous. In some cardiac cases there is a wide-spread pulmonic engorgement, with a tendency to exudation into the lung-vessels and smaller bronchial tubes. Under such circumstances the local irritant action of ether upon the mucous membranes is so deleterious that the surgeon is placed, as it were, between Scylla and Charybdis, and may in an individual case have great difficulty in deciding what is best. Some surgeons prefer under these circumstances the so-called *A. C. E. Mixture*, which is, however, of very doubtful advantage (see page 109—note). A better mixture consists of

six parts of ether and one of chloroform. Chloroform is especially dangerous when orthopnœa exists ; it is doubtful whether in such a case its use is ever justifiable.

Disease of the Respiratory Apparatus.—The existence of severe organic disease of the lungs seems to be a less serious bar to the use of anæsthetics than would be naturally expected. Of all the chronic pulmonic affections, probably emphysema, associated as it so frequently is with weakness of the right heart, causes the most solicitude to the anæsthetizer. The irritant local action of ether is an important element when the lining membrane of the tubes or air-vessels is seriously implicated ; indeed, our own opinion is very positive that in some of the deaths which have occurred in persons with diseased kidneys from œdema of the lungs directly after etherization the cause of death has been the local irritant action of the ether.* It would appear also that wide-spread organic changes in the lungs sometimes so interfere with the absorption of ether that it becomes exceedingly difficult to produce complete anæsthesia. The dictum of Hewitt, that in extreme emphysema, in chronic bronchitis attended by expectoration and dyspnœa, and in advanced pulmonary phthisis, chloroform or some other mixture containing chloroform should be employed, is, we believe, correct.

In all cases of lung disease it is important to remember that the more chronic the disorder the less important is it as a contra-indication to the use of an anæsthetic, and that anæsthetics are especially badly borne when there is acute or subacute pulmonary disease. Only under the most urgent circumstances should anæsthesia be attempted when in an acute pulmonary disease the symptoms are of sufficient intensity to produce even slight dyspnœa. In recent pleurisy or pleuro-pneumonia, with any embarrassment of the respiration or duskiness of the countenance, anæsthetization is attended by very grave risk.

In obstructive laryngeal disease, or when contraction of the lumen of the trachea, either from within or without, produces dyspnœa, the greatest caution must be exercised in the use of the anæsthetic. Under these circumstances the chances of ether increasing the mechanical asphyxia by

* *Ether Pneumonia.*—Severe and even fatal *pneumonia* has so frequently followed the use of anæsthetics that the possibility of its occurrence must be considered one of the serious dangers of anæsthesia. Allowing that particles of food may enter the lungs during the narcosis and produce inflammatory changes, there has been a tendency to believe that ether pneumonia more frequently follows the use of ether than of chloroform, and is due to the local irritant action of the ether. The research of Richard Holscher[9] has led him to the conclusion that the pneumonia is really due to the inhalation of bacteria from the mouth into the lung, that there is practically no irritation during etherization of the bronchial mucous membranes by ether, and that the râles which were heard during the narcosis are due to the inhalation of saliva, which may largely be avoided by lowering the head, turning it to one side, and keeping the mouth as free as possible from the secretion. Any mechanical obstacle to breathing, according to Holscher, greatly increases the likelihood of the inspiration of saliva, and the consequent danger of pneumonia. According to our belief, this research, although extremely important and suggestive as pointing out one cause of ether pneumonia, does not disprove the deleterious effect of the irritant action of ether.

irritating the larynx or trachea are very great, so that chloroform is preferable; or chloroform may be employed at first, and ether given when the reflexes have been abolished by the obtunding of the nerve-centres. When the laryngeal obstruction is of the nature of a spasm and not of an organic change, the use of the anæsthetic is free from extraordinary danger; but it must be remembered that frequently in such cases there is more or less laryngeal irritation, so that chloroform is preferable to ether, —a conclusion which is strengthened by the necessity which often exists for the prompt action of the anæsthetic.

In certain cases the mechanical obstruction may be a tumor in the mouth or other lesion above the respiratory tract proper, but if the respiration be interfered with, the general principles just enunciated hold good.

Diseases of the Kidney.—So far as our reading goes, Thomas A. Emmet was the first to report cases of fatal urinary suppression produced by the inhalation of ether in persons suffering from chronic Bright's disease. His statements have been followed by reports of numerous similar cases, and led to the wide-spread opinion that ether should not be used when there was chronic disease of the kidneys. It is now, however, certain that chloroform is capable of causing severe renal irritation, and although renal disease must be considered a contra-indication to the use of any anæsthetic, the choice of the surgeon may properly lean towards ether.

Albuminuria may be considered a sufficiently accurate evidence of renal irritation to enable the practitioner to use it as a working test. A large number of studies as to the effect of anæsthetics upon the urine have been made by different clinicians. Eisendrath[31] states that albuminuria was produced in his cases,—25 per cent. by ether, 32 per cent. by chloroform; and casts were found in 28.3 per cent. after ether, 21.4 per cent. after chloroform. In Wunderlich's studies the results were 24.6 per cent. after ether, 34.8 per cent. after chloroform.* Ogden found tube-casts in 70 per cent. of etherizations. Statements of other investigators, whom we shall not quote in detail, indicate that the occurrence of distinct albuminuria after anæsthesia in persons with sound kidneys is less frequent than these statistics would indicate; but all the statistics strongly point towards the opinion that, whilst both ether and chloroform seriously affect the kidneys, ether is less dangerous than is chloroform. These clinical conclusions are certainly borne out by the results obtained in animals by various investigators.

The choice of the surgeon between the two great anæsthetics should, in most cases of renal disease, be influenced by the existence of secondary effects of the disease. If, for instance, in any case there were pronounced degeneration of the heart-muscles, the selection should fall upon ether. If there were any reason, on the other hand, to believe that there was in

* For elaborate articles on the action of chloroform on urine and kidneys, see F. Nachod (*Archiv f. Klin. Chirurgie*, 1890, li.). See also Babacci and Bebi (*Il Policlinico*, 1896, iii.), in which the conclusion is reached that, although ether produces slight changes in the kidneys more frequently than does chloroform, it never causes such profound alteration.

the case a tendency to serous exudation, the danger of the production of œdema of the lungs by ether through its local irritant action would be sufficient reason for the selection of chloroform. In doubtful cases of cardiac complication it might be good practice to commence the anæsthesia with ether, and, when once its stimulating action was established, to continue the narcosis by the use of chloroform.

Under the present heading may be mentioned the important observations of E. Becker,[10]* who, in two hundred and fifty experiments made with ether, ethyl bromide, and chloroform, found that the anæsthesia was followed by pronounced *acetonuria*, which he believed to be due to increased destruction of albumin. In three diabetics he noticed great increase in the amount of acetone in the urine,—an indication that under certain circumstances diabetes should be considered a contra-indication to the use of an anæsthetic.

ADMINISTRATION.—The methods of the administration of chloroform and ether naturally differ. With ether the nearer the saturation of the air is reached the quicker will be the induction of anæsthesia, and the effort has generally been to give the anæsthetic in as concentrated a form as possible. It is certain, however, that the disagreeable symptoms of the first stage of ether may be largely avoided by the primary use of a very much diluted vapor.

According to Snow, at 80° F. air saturated with ether contains seventy-one per cent. of the vapor.

Ether was formerly habitually given by making out of stiff paper or card-board a cone that would fit, when a saturated napkin had been placed into it, over the nose and mouth of the patient. Though by this method anæsthesia is rapidly insured, the discomfort of the patient is brought to a maximum. Much better results are reached by laying five or six thicknesses of surgical gauze lightly over the mouth and nose of the patient, and then dropping from a properly prepared bottle the ether, drop by drop, upon the gauze just below the nostrils.

Ether is also given by means of various inhalers; the so-called "closed" inhalers, in which there is only a small supply afforded of atmospheric air, are, in our opinion, exceedingly dangerous; whilst the Allis inhaler offers the perfection of method for the production of ether anæsthesia.† In Europe various inhalers are employed for the administration of chloroform; but in this country they are rarely, if ever, used. A napkin or a few folds of surgical gauze may be laid over the nostrils and

* Confirmed by Luzzati (*Comment. Clin.*, 1895).

† The inhaler invented by O. H. Allis is based upon the theory that the patient to be etherized should be supplied with an abundance of air, impregnated with the vapor of ether. It consists essentially of a series of foldings of muslin on a wire framework, arranged almost like the gills of a fish, so as to allow the air to pass freely through, but everywhere to come in contact with the ether. It should be placed upon the face of the patient dry, and the ether gradually poured on from a so-called "Polyclinic" bottle, which has two fine tubes through the cork, one short, to admit air, and one reaching to near the bottom, so that the ether can be poured through it in a fine stream.

mouth, and the chloroform dropped upon this. Whatever plan be employed, it is of vital moment that the vapor be well diluted ; not more than three and one-half per cent. of it should be contained in the inspired air.

The use of ether at night requires care. We have seen a flame, by lighting the vapor, pass over eight feet and set on fire the ether sponge and the patient. As the vapor of ether is heavier than air, if the anæsthetic be used at night the light should always be elevated. The administration of chloroform at night is also not free from danger. Attention has been called by various practitioners to violent catarrhal inflammations of the respiratory passages, and even to fatal pneumonias, which have been produced by the use of chloroform in confined rooms with artificial light. It has been shown by the analyses of Bosshard and others that, under the circumstances mentioned, by the decomposition of chloroform there is liberated free chlorine and also phosgene gas, to which probably are due the local inflammations.*

ACCIDENTS.—In 1848 Duméril and Demarquay[11] showed that during anæsthesia there is a reduction of temperature. This has been confirmed by Bouisson[12] and by Sulzynski.[13] This fall of temperature may, when narcosis is prolonged, amount to 2° F. Whether this fall of temperature be, as asserted by Scheinson,[14] due to a lessened production of the bodily heat, or whether, as seems to us more probable, it be the outcome of an increased dissipation of bodily heat, is of no practical importance to the surgeon. The immediate lesson is, that prolonged severe operation should be done in very hot rooms, and that when the bodily heat falls it should be maintained by the external use of heat, in some cases even by the employment of a hot-water mattress.

In practical anæsthesia it is a matter of the gravest importance to recognize the coming on of accidents. Cessation of respiration may be sudden ; more usually it is gradual. Irregularities of respiration, and increasing shallowness of respiration appearing during the *advanced stages* of anæsthesia, are most urgent signals for the withdrawal of the anæsthetic and the use of prompt measures for relief. Failure of the pulse is, of course, of still more serious import, but it is often so sudden as not to be noticed immediately. It is always accompanied or immediately preceded by a peculiar change in the facial color or expression, and the anæsthetizer should therefore not merely watch the pulse, but especially the face. The measures which formerly were chiefly relied upon in the treatment of chloroform accidents are : dragging out of the tongue, inverting the patient, slapping with wet towels for the purpose of arousing reflex respiration, and the hypodermic use of ether, alcohol, ammonia, and certain other drugs.

Hypodermic injections of ether, though frequently employed, are so absolutely absurd that one wonders at the fatuity of surgeons. Ether

* Consult Zweifel (*Berl. Klin. Wochensch.*, 1889), D. R. Paterson (*London Practitioner*, xlii.), and Brandenberg (*Corr. Bl. f. Schweizer Aerzte*, 1897, xxvii. ; *Arch. f. Hygiene*, 1891, xiii.).

in the blood acts as ether, whether it finds entrance through the lungs, through the rectum, or through the cellular tissue; and the man who would inject ether hypodermically into a patient who is dying from ether, should, to be logical, also saturate a sponge with the ether and crowd it upon his unfortunate victim.

The drug which has probably been most largely used is alcohol. Owing to the closeness of the relations of alcohol to ether and chloroform, H. C. Wood many years ago taught that the administration of alcohol during anæsthesia was a doubtful procedure; subsequently, R. Dubois[15] determined that in the alcoholized animal much less chloroform is required to kill than in the normal animal. Then H. C. Wood experimentally proved* that alcohol injected into the vein of a dog whose heart is depressed by chloroform, if in sufficient dose to exert any perceptible influence, always increases the cardiac weakness, or, if in considerable dose, immediately paralyzes the viscus. Without doubt patients have been killed by alcohol given to relieve cardiac failure during anæsthesia. Experiments similar to those with alcohol just spoken of were made: with ammonia, which was found usually to have a distinct, though very fugacious, influence upon the chloroformed heart; with digitalis, which was found to have a very powerful stimulant influence upon the heart and blood-pressure; with amyl nitrite, which failed to produce any pronounced influence for good; with caffeine, which seemed to have little or no power; and with strychnine, which had some slight influence upon the blood-pressure, but an enormous one upon the respiration of the chloroformed animal. Thus, a respiration which had practically ceased for ten seconds, suddenly, under the influence of an injection of strychnine, became very quick and full. Cocaine was not tried, but studies made with it since upon chloralized dogs indicate that it has distinct value, especially when given with the strychnine.

In the first edition of the present treatise it was written: "Whenever there is any failure of the heart's action, as is nearly always the case, the body should be laid at an angle of forty degrees, with the head downward, so as to favor the passage of arterialized blood to the brain" (E. L. Holmes[16]). Some years after this the method was asserted in France to have just then originated with Nélaton. It undoubtedly has value. The body of the animal whose circulation has been paralyzed by chloroform acts in a measure like a tube filled with liquid. When the feet are raised above the head there is a marked increase in the blood-pressure in the carotid, with decrease in the blood-pressure in the femorals; and when, on the other hand, the feet are dropped below the head, the blood-pressure fails in the carotid, but rises in the femorals. The respiration is not affected by the procedure, but a heart which has entirely ceased will often suddenly resume its work when the feet are elevated. Inversion causes the blood which has collected in the extremely relaxed ab-

* See H. C. Wood's address, Berlin Congress, 1881.

dominal vessels to flow into and distend the right side of the heart, and this distention may have sufficient influence to stimulate into action a failing organ.

The one measure which H. C. Wood found in his experiments upon fatally anæsthetized animals to surpass, in practical efficiency, all others combined, was artificial respiration, by means of which animals were frequently resuscitated after all cardiac and respiratory movements had apparently ceased.

In the light of all our present clinical and experimental knowledge, the following rules may be formulated as embodying the treatment of the accidents of anæsthesia :

First. Unless the pulse be beating actively, partially invert the body of the patient.

Second. Place the index fingers of each hand upon the corresponding cornua of the hyoid bone, whilst the middle fingers rest upon the angle of the jaw, and then press forward and upward, the same force serving to extend the head upon the neck ; if this fail to open the glottis, by means of a tenaculum, thrust far back into the base of the tongue, draw it forward.*

Third. Make a momentary effort to stimulate respiration by slapping the chest, by douching with cold water, or by the method, suggested by Hare, of pouring a little ether on the bared abdomen, so as to get the effect of cold. Do not waste time, if respiration has failed, in any of these attempts.

Fourth. Avoid the use of all drugs except digitalis, strychnine, and cocaine given hypodermically, and sometimes ammonia by the mouth.

Fifth. Begin artificial respiration at once, even when the heart is primarily affected, as the great hope of the patient lies in the removal of the anæsthetic from the residual air of the lungs, so as to facilitate its escape from the blood.

It is evident that the ordinary methods of practising artificial respiration in man are exceedingly imperfect and feeble, and that in the accidents of anæsthesia so-called *forced artificial respiration* should be at once employed (see address on *Anæsthesia*). The principle of forced artificial respiration consists simply of pumping air into the lungs by means of a bellows. Fell's apparatus is efficient, but unnecessarily complicated ; a simpler one is described in a foot-note.† When no apparatus is at hand,

* Benjamin Howard asserts that the common practice of drawing out the tongue has no influence in raising the paralyzed epiglottis, which he affirms can be accomplished only by extending the head and neck ; but in the elaborate experiments made in the University laboratories by Hobart A. Hare and Edward Martin it was demonstrated that the method of Howard is inferior to that given in the text (*Medical News*, 1889).

† *Apparatus for Artificial Respiration.*—Fell's apparatus consists of a pair of foot-bellows by which air is forced into a receiving chamber, which is connected with an apparatus for warming the air, and a valve which can be opened and shut by a movement of the finger. This valve, in turn, leads to the tracheal tube. When the valve is opened the air rushes through the chamber into the lungs and expands them ; the finger is lifted, the valve shuts, the lungs contract, and so the respiration goes on.

A much simpler, cheaper, and probably equally efficient apparatus may consist

forced insufflation by breathing into the patient's mouth may be tried. A. E. Prince[17] reports a case saved in this way.

In using this apparatus, the mask should be first tried, care being exercised to see that the tongue is well drawn forward and held in place by a thread through it, and that the epiglottis is kept open. If the lungs do not fully expand, the intubation-tube may be used. Whether the mask or the intubation-tube be employed, the lungs should be thoroughly but slowly expanded by each stroke of the bellows, and a respiratory rate of about sixteen to twenty a minute be steadily maintained. It is essential to free the lungs and blood of chloroform as rapidly as possible, by quickly changing the residual air of the lungs ; but of course due care must be exercised that no force sufficient to rupture air-vesicles be employed. When the symptoms are protracted, and the bodily temperature falls, the bodily heat must be maintained by external warmth, and the temperature of the room, unless the air entering the lungs be artificially heated, should not be less than 80° F.

Besides the methods of procedure in anæsthetic accidents whose value is well established may be mentioned the opening of the jugular vein after cardiac arrest during chloroform anæsthesia, as recommended by Waterhouse and Gibbs,[18] a procedure of very doubtful utility ; tracheotomy, as employed by Poncet and De Laup,[19] on the theory that cool, fresh air striking the trachea should reflexly excite respiration ; and the injection of warm normal salt solution into the vein, which is said to have been long practised in anæsthetic syncope in Russia, and whose value has been sustained in a series of experiments upon animals by S. Gomberg.[20]

After-Effects of Anæsthesia.—Many years ago Liman affirmed that at least some of the deaths following operations which have been attributed to the operative procedure have been due to the chloroform. The correctness of this view we have demonstrated by having such deaths occur in the lower animals after both chloroform and ether when there has been no surgical operation, the animal regaining consciousness, but by and by passing into a condition of profound asthenia, with loss of all functional power, ending in death. These deaths are due to anatomical changes in important organs.

About a decade since it was shown by Ungar and by Path,[21] that when in the dog narcosis is maintained for a length of time by the inhalation of chloroform, there is produced a fatty degeneration which is usually most marked in the liver and kidneys and in the heart-muscles, but may be pronounced in the spleen, in the general epithelial tissues, and in the voluntary muscles. These researches have been confirmed in their general results in numerous experiments upon animals by Strassmann,[22] by Ostertag,[23] and by Kast and Mester.[24] Tedeschi,[25] in an elaborate

simply of a pair of bellows of proper size, a few feet of india-rubber tubing, a face-mask, and two sizes of intubation-tubes; there should also be set in the tubing a double tube, with an opening similar to that commonly found in the tracheal canula of the physiological laboratory, so that the operator can allow the escape of any excess of air thrown by the bellows. In a recent article (*Journ. Amer. Assoc.*, 1892, xix.) Fell insists on the superiority of his apparatus, and possibly in a large surgical clinic it might be well to provide his rather complicated mechanism.

study upon guinea-pigs, has found that the first anatomical alteration produced by chloroform consists of cloudy swelling which may go on to degeneration, or may subside; and that even when a considerable degree of apparent fatty degeneration has occurred recovery is possible. He also finds that these alterations were most severe in the nervous system, which is somewhat contrary to the general opinion. Botscharoff[26] and S. Schmidt (*Archiv f. Anat. u. Physiol.*, 1897) assert that they have demonstrated alteration of the heart-ganglia, especially vacuolation of the cells, after prolonged chloroformization.

Eugene Fraenkel[27] found in four human subjects, dying after prolonged chloroformization, wide-spread necrotic degeneration, especially affecting the heart-muscles and the epithelium of the kidney. As these observations have been abundantly confirmed (Bandler,[28] Ambrosius,[29] and our own laboratory), it must be considered proved that chloroform has the power of producing tissue degeneration, ending in death.

The possibility of after-effects from the anæsthetic should certainly influence the choice of surgeons.

According to Desgrez and Nicloux, chloroformization of the lower animals causes a great increase in the amount of carbon monoxide in the blood. As this substance is produced by the decomposition of chloroform by an alkali, and as Desgrez and Nicloux have failed to find that it is increased in the blood by etherization, it probably is produced in the blood by the destruction of the chloroform, which destruction must be accompanied by the formation of various chlorine compounds.

On the other hand, the destruction of ether in the system can scarcely yield other than harmless educts, so that, *a priori*, after-effects are much more probable from the use of chloroform than from ether. This probability is strongly confirmed both by experimental and clinical evidence. As the result of many years' experience in the physiological laboratory, we are very sure that after-deaths are much more frequent in animals which have been chloroformized than after ether.

In experiments performed by William Carter and H. C. Wood in the University laboratory, tissue-changes similar to those caused by chloroform were found in the dog after etherization. These studies have been corroborated by the researches of Ferdinand Schenk[30] and of Tedeschi. Again, in a woman whose death occurred twenty-four hours after a prolonged etherization in the University Hospital, without obvious cause, wide-spread tissue-changes were found. It is certain, however, that chloroform acts far more powerfully upon tissues than does ether, so that, whenever a prolonged anæsthesia is necessary ether should always be selected.

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FAMILY III.—SOMNIFACIENTS.

In the family somnifacients are placed in this treatise those drugs whose chief use in practical medicine is for the production of sleep. The alkaloid hyoscine is a practical hypnotic : it belongs, therefore, to the present family ; so that, although it is derived from a mydriatic drug and is in nature associated with the mydriatic alkaloid hyoscyamine, we consider it in the present chapter, whilst the crude drug, hyoscyamus, is discussed among the Delirifacients.

OPIUM. U.S.

The inspissated juice of the unripe capsules of the Papaver somniferum, or poppy. It is obtained by incising the capsules with a small, sharp knife, and twenty-four hours afterwards scraping off the exuded juice with a blunt blade. Opium is produced in various parts of the world,—chiefly in Turkey, Asia Minor, Persia, and India, but also to a very slight extent in England, Germany, and the United States. Our market is almost exclusively supplied from Asia Minor, with the variety known as *Smyrna* or *Turkey Opium.* This occurs in masses from the size of the fist to that of a child's head, irregularly globular, more or less flattened, covered externally with the capsules of a species of Rumex or dock, hard externally, softer and of a reddish-brown color within, and of a strong narcotic odor and taste.

On exposure to the air, opium becomes hard and brittle, and is readily reduced to a powder of a yellowish-brown color. It yields its principles to water, alcohol, and diluted acids, forming dark brown solutions. It is a very complex body, containing the alkaloids morphine, codeine, narceine, narcotine, thebaine, papaverine, porphyroxine, cryptopine, meconine, opianine, and paramorphine, besides meconic, thebolactic, and sulphuric acids, extractive matter, gum, glucose, fixed oils, a volatile odorous principle, and other substances of no importance.

Local Action.—The local action of opium and its chief alkaloid appears to be purely sedative.

Elimination.—After its absorption morphine probably passes into all the secretions ; after its hypodermic administration it has been detected in the gastric juice by Orlt,[1] and in the saliva by Rosenthal,[2] but it chiefly escapes with the urine, in which it has been found by Hilger (quoted by Gscheidlen), Bouchardat,[3] Lefort,[4] Kausmann,[5] Eliasson,[6] and Wormley.[7] Morphine is to some extent excreted from the salivary

glands as well as from the mucous membrane of the stomach, to be probably reabsorbed. This has been proved not only by experiments upon animals in which the morphine was injected subcutaneously, but also in the human individual (Rosenthal,[8] P. Binet,[9] Hamburger[10]). Elimination probably goes on slowly, as Wormley detected the alkaloid in urine passed three days after its ingestion, and in habitual opium-eaters morphine may be present in the urine seven days after the cessation of the habit.[11] A. Antheaume and A. Mouneyrat[12] detected morphine in the body of an opium-eater who had died fourteen days after the last dose. It was found most abundantly in the liver, next in the brain, next in the kidneys.

Physiological Action.—When opium is taken in such dose as to produce its mildest physiological effects, it exerts a quieting influence, inducing a peculiar dreamy condition of bodily comfort and happy content, during which images and ideas float before the mind, and by their endless and effortless repetition shorten the time, which seems to lose itself in rest. It is commonly asserted that there is a stage of the action of opium in which the activity of the mental faculties is exalted. This may be so in some persons, and especially in those who have accustomed themselves to the use of the drug as a stimulant; but our experience is that in those who do not habitually take opium true mental power is, during all the stages of the action of the drug, diminished rather than increased. The state induced is the fabled calm of the lotus-eater rather than the energetic activity of production. Even in those who are accustomed to the use of opium as an aid to work, it is probable that the imagination rather than the reasoning faculty is excited by it. After a length of time, varying according to the idiosyncrasies of the patient and the dose of the drug, the condition which has been noted gradually passes into sleep,—either light and dreaming, or natural, or heavy and deepening into stupor, according to the amount of the drug ingested. On awakening, the patient may return at once to his normal condition, but very often he experiences a state of depression, as shown by languor, a little headache, nausea, or even vomiting, which may last for some hours.

After very large doses, the first stage of the action of opium is very short, or it may be entirely wanting, sleep coming on almost at once. Thus, we have seen deep coma produced in three minutes by a hypodermic injection of morphine. The symptoms of the second stage of opium-poisoning closely resemble those of congestion of the brain: the pupils are strongly contracted; the face is more or less suffused, often deeply cyanosed; the pulse full, slow and strong; the skin generally dry and warm; the respiration slow and deep, and, it may be, stertorous; unconsciousness is apparently complete, though generally the subject can be aroused by violent shaking or by shouting in his ear, but relapses at once when left to himself. When the patient is aroused, the respirations become more rapid, and the skin often regains almost at once its normal color. Death very rarely occurs during this second

stage of opium-poisoning. When the symptoms do not gradually ameliorate, the third stage, that of prostration, is developed. The coma is now profound, and to arouse the patient may be impossible ; the pupils are absolutely contracted or, as death approaches, are widely dilated ; the respirations are distant, slow, feeble, and imperfect, and often interrupted by intervals of death-like quiet ; the countenance is at once pallid and cyanosed ; the pulse continually grows more rapid and more feeble ; the cold and moist skin finally becomes covered with a clammy sweat. Even yet the patient may recover, the return to life being very gradual ; when death occurs, it is by failure of the respiration, but amid an almost complete extinguishment of the vital functions.

Although the symptoms which have been narrated are those usually produced by opium, yet in certain individuals the drug provokes quite different phenomena. Thus, not infrequently there is an excessive depression following the opiate sleep. This state is seen most frequently in neuralgic or neuropathic females. The symptoms are a feeling of weakness and prostration, often accompanied by chilliness, dull headache, and giddiness, but especially marked by intense nausea and repeated vomiting. Very frequently vomiting does not take place so long as absolute rest in the horizontal position is maintained : indeed, an almost diagnostic sign of this affection may be found in the fact that the stomach is quiet so long as the patient keeps the head upon the pillow, but the distress occurs at once upon rising up. In some cases this condition of depression even replaces the normal second stage, so that opium, instead of inducing quiet sleep, will provoke alarming depression and vomiting, either with or without drowsiness. Thus, cases have been reported in which one-fourth of a grain, or a somewhat greater quantity, of morphine, hypodermically injected, has been followed at once by syncope, with struggling for breath, and apparently imminent or even present death.* A rarer idiosyncrasy exists in those persons who are rendered by opium very delirious, it may be even wildly so. In certain cases of opium-poisoning, partial or complete convulsions have occurred amidst the more usual phenomena.† Severe itching of the skin is a common phenomenon when the action of opium is going off, and there are persons in whom such violent erythema is produced even by therapeutic doses as to forbid the use of the drug (case, *Wien. Med. Presse*, xxiv. 568) ; R. V. Jaksch[13] reports temporary blindness as produced by opium.

Opium appears to act so differently upon the lower animals than upon man that it seems necessary to discuss the former action by itself.

As long ago as 1826 Charvet[14] stated that opium in the invertebrata caused progressive loss of power in the contractile tissue, ending in death ; in fishes, paralysis and convulsions ; in birds and mammals, paralysis, convulsions, and stupor.

* See Report of the Committee on the Hypodermic Method of Injection, *Medico-Chirurgical Transactions*, i. ; see also *Medical Times and Gazette*, 1868, cases reported by Braine and by Roberts.

† Cases, *Brit. Med. Journ.*, 1876, ii. 496 ; *Pacific Med. and Surg. Journ.*, July, 1876.

In the frog, opium and morphine act similarly, producing primarily a condition of violent tetanus, with great increase of the reflex activity, ending, if the dose have been large enough, in a progressive paralysis with disturbed respiration, and finally cessation of the same. W. Baxt[15] states that when a very minute dose is used (15.25 milligrammes) after a period of heightened excitability there is stupor with increased reflex excitability as it passes off. As was first shown by Kölliker, and abundantly demonstrated since, the tetanus is not prevented by section of the spinal cord, and, with the heightened reflex activity, is therefore due to spinal excitement. It is probable, however, as affirmed by Kölliker,[16] by Albers,[17] and by Meihuizen,[18] that some of the convulsions are epileptiform. Albers states also that convulsive movements occur in limbs after section of their nerves, a fact which seems to us very doubtful.

S. Weir Mitchell[19] has shown that birds, as represented by pigeons, chickens, and ducks, are very insusceptible to the toxic action of opium and its chief derivative, morphine. It appears to be impossible to kill a pigeon by opium given by the mouth, and of morphine from eight to fifteen grains are required to produce a fatal result; but when given hypodermically from two to three grains of the alkaloid suffice. The symptoms induced have been very uniform: they are unsteadiness, labored breathing, increasing signs of dyspnœa, *unaltered* pupils, and, finally, general convulsions and death. No true hypnotic effect has been observed, but a curious and very great rise of temperature just before death was noted in one case. As Flourens affirms that a single grain of the aqueous extract of opium will throw a sparrow into a profound stupor, it can scarcely be considered as proved that the drug acts upon all birds as upon those experimented with by Mitchell.

According to M. L. Guinard,[20] in the cat morphine produces violent hyperexcitability, great restlessness, agitation, hallucinations, dilated pupils, accelerated heart and respiration, from which the animal returns to its normal condition unless the dose have been very large, when tetanic convulsions develop.

Upon dogs* morphine acts very much as upon man.† In very many cases, if not in the majority, eight to ten grains of the alkaloid injected into a dog of moderate size will cause deep sleep, amounting to coma, so that the animal will remain in any position in which he may be placed. The length and depth of this sleep are, of course, proportionate to the dose: when at all profound, it is accompanied by marked insensibility to pinching and other forms of external irritation. A repetition of irritation, and especially a sudden loud noise or shaking, will, however, arouse the animal, precisely as in man. Indeed, sometimes the dog, even when comatose, seems more than normally sensitive to sudden noise, trembling and starting in an almost convulsive manner. After awaking, the dog shows unmistakable signs of nervous and psychical depression. In walking, the hind legs are dragged, as though semi-paralyzed; the eyes are haggard; the naturally brave animal cowers in a corner or seeks to hide himself, no longer recognizing his master, and does not return to his natural condition for many hours. After smaller doses the effects are proportionately less intense. It has been shown by Harley that in some dogs, precisely as in some people, morphine fails to exert its usual hypnotic action, but produces great depression, as evinced by faintness, prolonged nausea, and retching, interrupted only by intervals of dreamy delirious somnolency.

In the horse (Harley) two or even three grains of morphine hypodermically injected produce sometimes a slight drowsiness, sometimes no perceptible effect. Doses of from four to six grains cause great restlessness and accelerated pulse.

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* According to Joffroy and Serveaux (*Archiv d. Med. Exper. Anat. Path.*, 1898, x.), the fatal dose of morphine is: for dogs, intravenously 0.029 gramme per kilo, hypodermically 0.035 per kilo; for rabbits, intravenously 0.15 per kilo, hypodermically 0.25 per kilo.

† Harley, *The Old Vegetable Neurotics*, 107, London, 1869; Claude Bernard, *Archives Générales*, ii. 437, 6th series, 1864; J. I. Reese, *American Journal of the Medical Sciences*, Jan. 1871.

The mouth is moist, the temperature of the skin and its secretion increased; the animal paws continually, and treads about in his stall with an almost rhythmical movement. After twelve grains, Harley noticed in some cases very great excitement, as shown by marked increase in the rapidity of the heart's action, by muscular rigidity and tremors, and by the animal's walking rapidly to and fro, slobbering and sweating profusely. In another horse, after an immediate strong erection of the penis and copious emission of semen, heavy sleep came on, interrupted after the third hour by the usual symptoms of excitement. Thirty-six grains of morphine acetate caused in a powerful hunter deep comatose sleep, commencing in fifteen minutes and lasting for three hours, when it was replaced by intense restlessness and severe delirium, continuing for seven hours. During this time the animal was perfectly blind. Previously to these studies, Barbier had found that four drachms of the aqueous extract of opium produced violent tremblings, apparent insensibility to external irritants, convulsions without coma, and death. One hundred grains of morphine acetate killed a horse by convulsions in three hours.

In the mouse, according to the experiments of Harley, the first effect of an injection of from one-twentieth to one-twelfth of a grain of morphine is a tonic cramp-like contraction of the muscles, especially of the trunk, of such character that periods of forced rest alternate with a slow, laborious creep, which seems to originate not in the limbs but in the trunk itself. There is in this state no tendency to somnolency, but, on the contrary, an abnormal sensitiveness to loud sounds, which cause the mouse to resume for a moment active running movements. The breathing is irregular, the pulse accelerated, and finally stupor develops itself, and coma deepens into death by dyspnœa; or, otherwise, recovery, preceded by convulsive movements of the hinder part of the body, is gradually brought about.

In reviewing the action of morphine upon the lower animals, it becomes very evident that two classes of phenomena are everywhere discernible,—*i.e.*, the spinal and the cerebral,—and that the higher in the scale of life any given animal may be the more marked are the brain-symptoms. These cerebral phenomena are mostly sleep and stupor; but, as is well known, in some human individuals morphine acts as a delirifacient; and it seems very probable that the peculiar restlessness of the horse under the influence of the alkaloid is due to delirium, and not to spinal excitement.

When looked at in this manner, it seems to us that morphine does not act so differently as has been generally asserted upon the lower animals and upon man. The immensely higher cerebral organization of the latter, with the immensely greater sensitiveness which it involves, makes the man correspondingly more susceptible to the cerebral action of the drug: hence not only is he affected by much smaller doses of the alkaloid than are the lower animals, but as the spinal symptoms are triumphant in the frog because its spinal system is vastly more developed than its cerebral, so in man the cerebral symptoms mask the spinal because in him the brain is more developed than the cord. The two creatures—man and the frog—occupy the two extremes of the series; between them is probably to be found every gradation.*

* A curious corroboration of the views expressed in this paragraph is found in the following sentence taken from Althaus (*Diseases of the Nervous System*, New York, 1878, 135): "In infants, however, and also in the lower races of mankind, as in negroes and Malays, convulsions are observed after its [opium] ingestion."

The action of opium upon dogs and rabbits is sufficiently close to that upon man to enable us to reason from experiments upon the former as to the influence of the alkaloid upon the circulation and respiration in the latter. Indeed, so far as these functions are concerned, morphine appears to act identically in both instances.

Action on the Nervous System.—The cerebral symptoms produced by opium are without doubt due to a direct influence of the drug upon those cells which preside over intellectual action and consciousness. Opium is frequently spoken of as a cerebral stimulant, and some of the world's most famous writings have undoubtedly been produced under its influence. It appears, however, to be especially related with those tissues that are connected with imagination, so that it is the imagination rather than the reasoning functions which is affected by it. In this respect it is not so true an intellectual stimulant as is caffeine. It is undoubtedly a stimulant to the spinal cord ; but, as has already been shown, the cerebrum in man is so infinitely more susceptible to its influence than is the spinal cord that this spinal effect is rarely perceptible in man, even in toxic dose.

Nerves.—According to Gscheidlen,[24] morphine primarily increases and secondarily depresses the excitability of the motor nerves of the frog, the period of heightened functional activity not being demonstrable after enormous doses. Albers[17] affirms that depression may develop into complete paralysis of function, though Gscheidlen has never been able to verify this. Gscheidlen further asserts that the local application of morphine intensifies and protracts the excitability of an afferent nerve in strychnine-poisoning. No phenomenon of human poisoning by opium can be attributed to its action on nerve-trunks, but the relief of pain sometimes obtained by the local use of opium would indicate that in concentrated form it depresses the sensory fibres even of human nerves.

Action on the Circulation.—In man the circulatory phenomena are a slight primary evanescent acceleration of the pulse-rate (see Nothnagel[21]), succeeded by the characteristic slowing and increased fulness and force of the pulse, which is followed by a return to the normal pulse, or a great increase of rapidity and loss of strength, during the third stage. Gscheidlen has found in rabbits and dogs after the injection of morphine, first an increase in the pulse-rate, then a decrease, and finally return to the normal pulse, or else increased rapidity. Sphygmographic studies of the effects of small doses of morphine have been made with various results by several observers : undoubtedly in some individuals therapeutic amounts of the alkaloid depress sensibly the circulation, but, in agreement with Riegel and Preisendorffer,[22] it can scarcely be doubted that therapeutic doses have no sensible effect upon the circulation in the ordinary man. It has been found by M. L. Guinard[25] that in the dog morphine produces primarily a slight rise of the arterial pressure, followed by a fall during the period of narcosis.

The slow, full pulse of the second stage of opium-poisoning is due to

an action of the drug upon the inhibitory cardiac nerves, as may also possibly be in some manner the increased arterial pressure ; for Gscheidlen has experimentally demonstrated that after section of the vagi morphine is powerless to lower the pulse, and also that division of the nerves during the second stage of morphine-poisoning is followed by an extraordinary rise in the pulse-rate. That the peripheral ends of the vagi are stimulated was proved by the fact that cardiac arrest took place when the distal ends of the cut nerve were more feebly irritated than would suffice to affect the unpoisoned animal ; and that the inhibitory cerebral centres are stimulated was demonstrated by the instantaneous very great fall of the pulse-rate, amounting in some cases to one-half in less than half a minute, which ensued upon the injection of a large dose of the alkaloid into the carotid,—*i.e.*, into the brain and the inhibitory centres. The rapid feeble pulse of the third stage of opium-poisoning Gscheidlen found to be due, at least in a measure, to paralysis of the peripheral vagi ; for at such time stimulation of the peripheral end of the cut nerve was powerless to affect the heart.

The experiments of Gscheidlen also indicate that morphine exerts *first a slight stimulating, then a depressing influence upon the heart-muscle or ganglia*, since, after isolation of the viscus by section of the cord, sympathetic, and pneumogastric, life being sustained by artificial respiration, a large dose of morphine induced a momentary increase in the number of the cardiac contractions, followed by a marked decrease and finally extinguishment of the same. This conclusion is confirmed by Ringer and Sainsbury,[25] who found that opium first increased the power of the cut-out heart of the frog, then depressed it, and finally caused diastolic arrest.

The question of the action of morphine upon the vaso-motor system is of great interest, but cannot at present be fully answered. Gscheidlen believes that it first stimulates and then depresses it, and asserts that after the injection of a large dose the arterioles in the mesentery can be seen to contract, and later (third stage) to dilate. The objections to this sort of evidence are sufficiently stated elsewhere in this book ; and the rise of the arterial pressure, which he also adduces as an argument, may be accounted for without calling upon the aid of the vaso-motor nerves. While, therefore, it is probable that morphine does exert the influence he asserts for it, the question must still be considered as *sub judice :* that the vaso-motor system is not paralyzed even *in extremis* is shown by Gscheidlen's experiment (*loc. cit.*, 52), in which electrical stimulation of the cord at such time induced immediate rise of the arterial pressure. The action of morphine upon the brain is certainly independent of any action on the vessels.*

Action on the Respiration.—Death occurs from opium, in the great majority of cases, by failure of the respiration ; and that such failure is due to a direct action of the poison upon the respiratory centres in the

* Consult Binz, *Arch. f. Exper. Pathol. und Pharm.*, vi. 310; Vulpian, *Leçons sur l'Appar. vaso-moteur*, ii. 156.

medulla is proved by the fact that morphine affects the breathing of dogs and rabbits whose pneumogastrics have been cut as much as it does those whose nerves are entire (Gscheidlen).

The action of opium or morphine upon the elimination of carbonic acid has been studied by Boeck and Bauer[26] and by Chittenden and Cummins.[27] Their results are concordant in showing that the effect of the alkaloid upon carbonic acid production is in direct relation to its influence upon the muscular system. The elimination is increased when convulsions occur, but decreased when narcotic quietude is produced.

Action on the Pupil.—Since morphine locally applied does not affect the pupil, it follows that its constitutional action upon the latter is through the nerve-centres. It is probable, but has not, that we are aware of, been experimentally proved, that the contraction of the pupil is due to a stimulation of the oculo-motor nerve-centres, and that the dilatation of the pupil as death approaches is due to a paralysis of the same. Indeed, it cannot well be otherwise; for if the primary contraction were due to paralysis of the sympathetic, the secondary wide dilatation would be impossible; the dilating force—*i.e.*, the sympathetic—having been withdrawn, the pupil would not widely expand even if the contracting force—*i.e.*, the oculo-motor—were paralyzed.

In birds (S. Weir Mitchell) the pupil is not affected, probably for anatomical reasons (see *Atropine*). In horses it is widely dilated (Harley); and in dogs it dilates before contracting (Reese, apparently confirmed by Experiment No. 8, Harley, *loc. cit.*, 109), or sometimes remains unchanged (Harley). At present these anomalies cannot be explained.

Opium ordinarily checks all the secretions of the body, although this influence is capable of being modified by certain drugs so as to produce a sudorific action. By it the urinary secretion is habitually diminished, owing, as has been shown by Thompson,[30] to a direct action upon the kidneys. Retention, which after a full dose of opium is not rare, depends upon the blunting of the sensibility of the bladder.

Secretions.—Opium, and to a less extent morphine,* has a very pronounced influence upon the digestive tract, in many persons producing nausea, in all lessening the appetite and the activity of digestion and producing constipation. The disorder of digestion and the constipation are in part, at least, due to an arrest of secretion, probably both in the stomach and in the intestines; but they are also probably to some extent due to the checking of peristalsis, an effect which can often be demonstrated upon men, and which Nothnagel[28] and Ott[29] have demonstrated upon animals. Both Nothnagel and Ott affirm that the toxic dose of morphine

* Vamossy (*Deutsche Med. Wochensch.*, 1897, xxiii.) has endeavored to determine experimentally why opium causes constipation more than does morphine. He finds, however, that neither narcotine, thebaine, codeine, kryptopine, nor laudanine is equal in power of checking peristalsis to morphine; and that it is not probable that any of them are responsible for the constipating effects of the crude drug.

in the lower animals increases peristaltic movement, which affords a possible explanation of the diarrhœa sometimes seen in chronic opium-eaters. The checking of peristalsis appears to be due to stimulation of the inhibitory nerve apparatus ; the increase to paralysis of the same.

SUMMARY.—Opium is a cerebral stimulant, whose action soon passes into sedation and the production of sleep, and has the power of relieving pain in some way as yet not thoroughly known ; probably, however, by benumbing the perceptive centres in the brain. It acts upon the spinal cord of many of the lower animals as a stimulant, but in man its influence is not perceptible. It both slows the pulse and increases to some extent the force of the circulation by an action upon the inhibitory nerve-centres, probably both centric and peripheral, and by a slight stimulant influence upon the heart-muscle or its intrinsic ganglia. It is a centric respiratory depressant; it contracts the pupil by a centric action which is probably that of stimulation of the oculo-motor nerve-centres.

THERAPEUTICS.—The chief indications for the use of opium are considered below, *seriatim*. Nearly all of them flow evidently from the known physiological action of the drug ; others, however, although established by clinical experience, and undeniable, are not so plain in their philosophy.

1. *To relieve pain.* As an analgesic, opium is without a rival in the materia medica, except it be the anæsthetics. It is used to allay pain arising from any cause whatever, except acute inflammation of the brain, and is preferred to the anæsthetics whenever the pain has any permanency. In *painful spasm* it is especially useful, as it seems very frequently to quiet the motor as well as the sensory disturbance.

2. *To produce sleep.* Sleeplessness occurring in acute disease, and not dependent upon cerebral inflammation, may very frequently be relieved by opium. While it is often necessary to use the drug freely in such affections as *delirium tremens*, care should be exercised not to overwhelm the nerve-centres by enormous doses. In habitual sleeplessness great caution must be used in the employment of opium, not so much on account of the disturbance of digestion which it is liable to cause, as for fear of producing the "opium habit." Chloral is perhaps a more generally applicable hypnotic than opium. Be this, however, as it may, we have found the combination of morphine and chloral singularly efficient. In low fevers, adynamic delirium often coexists with sleeplessness, and is then best met by opium.

3. *To allay irritation.* In various forms of nervous erethism, opium is most valuable ; but when the affection is at all chronic, the dangers of the opium habit should not be lost sight of. On the other hand, in acute cases, as in the excitement which so frequently attends *hæmoptysis*, the drug should be used freely. In many cases of disease, opium is serviceable by sustaining the system against an irritation for the time being irremediable, by blunting the sensibilities. In this way it is useful in the advanced stages of *small-pox*, and in various surgical affections, in

which it also does good by allaying pain. In various local irritations opium is continually employed, as in *colic* caused by undigested food, and in *bronchitis* to quiet cough.

By allaying irritation and pain, opium affords relief in most cases of inflammation ; but in certain varieties of the affection it seems to do much more than this, exerting, in some way at present difficult to explain, a life-saving influence. In *peritonitis*, after due depletion, or in cases not requiring depletion, it should always be exhibited in large doses at regular intervals, in such a way as to keep the patient in a state of decided narcotism.

In severe *acute vomiting*, opium is one of the most reliable remedies. It is best used in the form of suppositories. Although, by checking secretion and peristalsis, opium usually causes constipation, yet when *obstruction of the bowels* is produced by spasm due to an irritation or inflammation, by relieving the latter the drug will sometimes act as a most efficient laxative.

4. *To check excessive secretion.* For this purpose opium is very largely employed in *diarrhœas*, and is very efficient either alone or in combination with various remedies. In *enteritis* and in *dysentery*, although no less frequently used than in diarrhœa, it is of service as an antiphlogistic and analgesic rather than by checking secretion. In *diabetes insipidus*, the combination of it and gallic acid has been much used, and is often effective.

In true saccharine *diabetes*, opium is of very great value in many cases, often ameliorating the symptoms, and, in conjunction with restricted diet, sometimes even effecting a cure. Of course, however, like all other known remedies in this disease, it most frequently acts simply as a palliative. It must be given in large ascending doses,—the patient for the time being indeed made an opium-eater,—a procedure justified only by the fatal nature of the malady.

5. *To support the system.* Opium appears in low fevers, and in various protracted adynamic illnesses, to afford actual support to the system in some way not as yet made out. This is especially the case when, from any reason, sufficient food to keep up life cannot be taken or retained. Opium is a valuable remedy for the purpose of protracting and rendering more comfortable life in the aged. When the bodily powers are failing, and various functional disorders are from time to time occurring, it is often possible to check, by the use of opium, attacks which, if allowed to obtain headway, would extinguish the flickering life. Further, in many cases of feeble very old and suffering people the habitual use of opium under careful restriction of the physician is not only justifiable, but necessary if life is to be maintained as long as possible. In such persons the danger of forming an opium habit which shall do injury is reduced to a minimum.

6. *As a sudorific.* In 1873 A. Loomis[31] stated that in acute *uræmia* large hypodermic injections of morphine would control the convulsions,

at the same time producing a profuse diuresis, which has been confirmed by Fiset.[32] The method of treatment has been largely followed, in some instances with very happy effect, but in other cases has apparently produced death. Whenever the kidneys are seriously diseased the free administration of opiates is attended by much danger, because the chief channel through which the opium alkaloids escape from the system is choked up. As a general sudorific opium is used almost exclusively in the form of Dover's powder. (See Dover's powder in Diaphoretics.)

TOXICOLOGY.—Sufficient has already been said concerning the course and symptoms of poisoning by opium in ordinary cases.* Sometimes in adults trismus and other convulsive manifestations are added to, or in a measure replace, the usual phenomena, and in children the drug appears at times to overpower the nerve-centres at once, so that the second stage is very much shortened or aborted, and symptoms of collapse, with unconsciousness, are developed very rapidly. The positive diagnosis of opium-poisoning from the symptoms alone is often impossible.† In some cases of congestion of the brain, or of apoplexy, or of uræmia, the phenomena are identical with those sometimes seen in opium-poisoning. We have thought that inequality of the pupils is proof that a case is not one of narcotism; but Taylor[33] has recorded its presence in opium-poisoning.

Treatment of Opium Poison.—Tannic acid is feebly antidotal to morphine, but it has been entirely displaced by potassium permanganate, which rapidly destroys the alkaloid by oxidation. The allegation that potassium permanganate is capable of following morphine into the blood and there destroying it is a physiological absurdity. It has further been experimentally shown that the hypodermic injection of potassium permanganate in morphine-poisoning is futile.‡ Nevertheless, during the whole narcosis, there should be repeated administrations of potassium permanganate by the mouth for the purpose of destroying morphine excreted into the stomach. Besides the administration of the antidote, the indications in opium-poisoning are to evacuate the stomach, to maintain respiration, and to keep up the circulation when failing. The first of these indications may be met in two different ways: by an emetic, and by the stomach-pump or tube used as a siphon. There is often in narcotic poisoning great difficulty in getting an emetic to act, owing to the obtunding of the sensibility of the nervous system by the drug. For this and other reasons, so palpable as not to need mentioning, only a prompt stimulant emetic should be used. Antimony, on account of its depressing influence, should always be avoided. *Mustard flour* is almost always to be had at once, and is very efficient. A heaped tablespoonful stirred up

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* For discussion of effect on nursling and fœtus when morphine is given to the mother, see *Amer. Journ. Obst.*, 1877.

† See *Philadelphia Med. Times*, iii. 593; also Wilks (*Med. Times and Gaz.*, 1863).

‡ See Leedom Sharp (*Therap. Gaz.*, 1895); also E. Q. Thornton and Charles A. Holder (*Therap. Gaz.*, 1897).

in a tumblerful of warm water should be exhibited as soon as possible, and, if it fails to act in fifteen minutes, should be repeated ; then a powder of thirty grains each of zinc sulphate and ipecacuanha may be given, to be repeated once or twice, at intervals of fifteen or twenty minutes. Large draughts of warm water should be administered in the intervals, and also between the acts of vomiting, so as thoroughly to wash out the stomach. The stomach-pump * is of no value when the solid drug has been ingested, but, if at hand, is preferable to emetics when a fluid preparation has been taken, because of the promptness and thoroughness of its results.

To maintain respiration is the ultimate object of all the measures which are commonly undertaken for the purpose of arousing the system in opium-poisoning. Unconsciousness in itself is of no moment, but as it deepens the sensibility of the respiratory centres grows less, and consequently the involuntary breathing is less rapidly or less perfectly performed. More than this, when at all awake, a patient suffering from opium-poisoning can be made to supplement the almost suspended automatic breathing by voluntary respiration, and every effort to induce him to do this should be used. It is often surprising how an apparently unconscious man can be made to breathe by a command shouted in his ear. To keep a patient awake, walking, flagellations with small, *fine* twigs, shaking, shouting, and various other methods which may suggest themselves, should be practised. Care should always be exercised not to carry these useful measures unnecessarily far, and perhaps add physical exhaustion to the natural prostration of the third stage. The strong faradic current offers a means of causing pain, and therefore of rousing the patient, without leaving bruises or other after-effects.

The cold douche is also an excellent method of rousing the patient and at the same time of especially stimulating respiration. The simplest method of application is to support the head and shoulders of a patient stripped to the waist over a common wash-tub, and to dash the water over the chest and head. The effect is much greater if ice-cold water and water a little hotter than the hand will bear (115° F.) be used in quick succession. Caffeine as an alkaloid, or, better, in the form of very strong tea or coffee, has some value. Doses of morphine otherwise lethal may be successfully combated by it. Atropine, as a respiratory stimulant, is of the greatest importance when there is evident failure of respiration (for discussion of its use, see the article on Atropine) ; and alcohol is to be employed in the stage of depression to sustain the arterial system.†

* The *siphon stomach-pump* may be extemporized by any one. It consists simply of an india-rubber tube three and a half to four and a half feet in length, of proper calibre, which is passed into the stomach. The external end being elevated, water is poured into it until the stomach is full; then, without the tube being allowed to empty itself, the external end is dropped, when, of course, the flow of water is reversed.

† Various drugs have been stated to be antagonistic to opium and cases of recovery reported: VERATRUM VIRIDE, *Cincinnati Lancet and Clinic*, 1879, iii. 458; *St. Louis Med. and Surg. Journ.*, 1879, xxxvii. 601; ACONITE, *New York Med. Record*, 1880, viii. For paper showing that caffeine in the lower animal is antidotal to morphine, see *Brit. Med. Journ.*, 1874, ii.

H. C. Wood found, in the laboratory, strychnine to act very powerfully as a respiratory stimulant in narcotized animals, and Clara Dercum[34] reports a case of opium-poisoning in which its use in very large doses apparently saved life. In bad cases of opium-poisoning the use of artificial respiration should not be too long postponed. In some cases the Sylvester method may suffice, but, as was first shown by Fell,[35] forced respiration (see page 116) should be resorted to whenever respiration fails. Fell has reported recovery obtained in this way after the ingestion of twenty grains of morphine. So long as any movement of the heart continues, the forced respiration should be steadily maintained. In some cases the lungs become filled with bronchial mucus. Under such circumstances good may be achieved by placing the patient in an inverted position. It is often essential to keep up the temperature of the body by artificial means. Lauder Brunton and Cash have found that the fall of temperature in the poisoned mammal is not prevented by placing the animal in a temperature a little below that of the body, and the ordinary methods used in the sick-room to heat the cooling human body are of very little service. The hot bath or a water bed, two-thirds filled with water of the temperature of 150° F., may be employed.

Opium-poisoning usually has no sequelæ, but *amaurosis*[36] and *glycosuria*[37] have been reported.

In regard to the amount of opium which will cause death, the smallest fatal dose in the adult on record is one-sixth of a grain of morphine.* According to A. Calkins,[38] four grains † of crude opium placed in the ear have caused death ; also four grains by the mouth in more than one case. According to the authority just quoted, out of twenty-nine reported cases in which a fluidounce of laudanum was taken, nine died. The maximum doses from which recovery has occurred without emesis are fifty-five grains of the solid opium and six ounces of laudanum. The death of an adult female has been attributed, with doubtful accuracy, to thirty grains of Dover's powder, given in divided doses.[39] Recovery is asserted to have occurred after the ingestion of eighteen grains of morphine without vomiting (William C. Chaffee).

For full details as to the results of the habitual use of opium or its alkaloid, the reader is referred to the treatise of Albrecht Erlenmeyer (*Die Morphiumsucht*). No confidence can be placed in the statements of the opium-eater, and it is essential for cure that such person be in a hospital or be confined to an apartment under the care of an absolutely reliable nurse, so that the orders of the physician can be strictly enforced. The basis of the treatment must consist in the withdrawal of the narcotic, and there are three distinct ways in which this can

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* A number of cases are now on record in which death has been produced in the adult by the hypodermic use of from one-sixth to one-half grain of morphine. Consult *Chicago Med. Examiner*, May, 1878; *Quart. Journ. Psycholog. Med.*, 1868, ii. 739; also *Bost. Med. and Surg. Journ.*, 1885, i.

† Taken from *Journal de Chimie*, 1831. Assuredly there is a mistake in this case.

be effected. First, the opium may be suddenly taken away ; secondly, it may be taken away rapidly, but not suddenly ; thirdly, it may be withdrawn very gradually. The first of these methods is undoubtedly in most cases efficient, but is often attended by grave danger of collapse, and has no distinct advantages over the plan of rapid withdrawal. The time required for the very gradual withdrawal of the remedy is too great for practical purposes, and the sufferings of the patient are too long drawn out. Unless the daily dose has been extraordinary or the patient is in a very feeble condition, it is entirely safe to withdraw the narcotic entirely in from seven to twelve days. A convenient plan is to direct that a solution of morphine or opium be prepared, and whenever a dose is taken out an equivalent amount of water be added. The chief symptoms that follow the rapid withdrawal are excessive malaise, insomnia, complete loss of appetite, vomiting, diarrhœa, and great feebleness. We have never yet seen a case in which these symptoms were so uncontrollable as really to cause alarm for the safety of the patient. Much may be done by proper feeding. The food should consist of highly nutritious, stimulating, and easily digested articles, and in severe cases should be liquid, such as milk, rich soups, etc. When the circulation fails, alcohol may be used, and much relief may be afforded by massage, and often by simple rubbing of the patient. General electrical stimulation and faradization of the muscles is often useful, not only by its effect upon the circulation, but also by distracting the attention of the patient from his sufferings. The use of the alkaloid cocaine as a stimulant has been recommended. Good results may be obtained from the free internal administration of the fluid extract of coca, but the use of hypodermic injections of cocaine seems hardly justifiable, as the danger of setting up the cocaine habit is too great. If gastro-intestinal irritation exists, bismuth may be administered freely. The diarrhœa is usually controllable by mild vegetable astringents, especially if combined with sulphuric acid. If the bodily temperature falls at all, it must be maintained by external warmth. Potassium bromide, ammonium valerianate, Hoffmann's anodyne, and other similar feeble nerve-sedatives may be employed and give some comfort. Moral support and stimulation are essential, and massage or other device which aids in passing the time of suffering is most beneficial.

ADMINISTRATION.—When it is desired to produce very decided narcotism by the use of repeated doses of opium, the drug should *always be given in liquid preparation*, since opium pills sometimes become very hard and undergo solution so slowly that their accumulation in the alimentary canal is possible. On the other hand, in diarrhœas, or in sickness of the stomach, old opium pills are thought by some to act better than do more soluble forms of the drug.

Many persons cannot take opium on account of the very great secondary nausea and depression which it produces. It has been supposed that these disagreeable after-effects are due to the narcotine in opium ; but this can hardly be, seeing that they often follow the use of the pure

alkaloid, morphine. The deodorized tincture of opium agrees with some individuals better than any other preparation of the drug ; and, as first pointed out by Da Costa, by giving a drachm of potassium bromide with twenty-five drops of it, the after-effects of the narcotic are often entirely avoided. In many neuralgic women the knowledge of this fact is an inestimable boon ; in others the unpleasant symptoms are not averted by the bromide.

Children always bear opium very badly,* and to them only the weaker liquid preparations should be given. Dover's powder should especially be avoided. It is probable that in its manufacture on the large scale the ingredients are sometimes not thoroughly mixed : at least we have seen cases in which the symptoms caused by it were seemingly so out of proportion to the dose as to suggest that more than the official amount of opium was present.

In *acute vomiting* from any cause, in *dysentery*, in *strangury* and other irritations of the urino-genital organs, great advantage is often to be gained from the use of opium by the rectum. Suppositories made out of the extract (gr. ss to i), or enemata of laudanum (gtt. xxx to xl), may be used in these cases. The latter should be made by adding the narcotic to a tablespoonful of starch-water.

The dose of opium for an adult is from one to two grains ; for a child a year old, one-twenty-fourth of a grain. The U. S. Pharmacopœia directs that opium in its normal moist condition should contain not less than nine per cent. of morphine, and that dried powdered opium (Opii Pulvis, U. S.), out of which the preparations are made, should contain from thirteen to fifteen per cent. of the alkaloid.

The solid preparations are—the deodorized opium (Opium Deodoratum, U. S.), containing from thirteen to fifteen per cent. of opium, made by depriving powdered opium of all substances soluble in ether, dose, one to two grains (0.06–0.12 Gm.) ; pills of opium (Pilulæ Opii, U. S.), containing one grain each of powdered opium (0.065 Gm.) ; watery extract (Extractum Opii, U. S.), containing eighteen per cent. of morphine, three-quarters of a grain (0.05 Gm.) are about equal to one grain (0.065 Gm.) of powdered or deodorized opium, and on account of its being the most fixed in its strength of any of the solid preparations of opium, as well as of its being free from the noxious constituents of opium, and of its solubility favoring prompt absorption, it is the most useful and reliable of all the solid preparations of the drug ; Dover's powder (Pulvis Ipecacuanhæ et Opii, U. S.), one part of opium, one part of ipecacuanha, eight parts of sugar of milk.

Paregoric (Tinctura Opii Camphorata, U. S.) has in every fluid-ounce 1.85 grains of opium, besides benzoic acid, oil of anise, and camphor ; in consequence of the last ingredient, it is more constipating than the

* In a babe a day old, one minim of laudanum (E. Smith, *Lancet*, 1854), and in one aged nine months, a few drops of paregoric (Wood, *Bost. Med. and Surg. Journ.*, 1858), are said to have proved fatal.

other preparations of opium, and hence is preferred in diarrhœa-mixtures. It is also much used in cough-mixtures. Dose, f℥i to f℥i (3.75–30 C.c.). The other liquid preparations all *now* represent ten per cent. of powdered opium by weight, and may be given in doses of ten to fifteen minims (0.6–0.9 C.c.). The deodorized tincture (TINCTURA OPII DEODORATI, U. S.) contains no narcotine, and none of the odorous principle of opium. It therefore is less apt to cause nausea than are the other preparations. Its drop almost equals the minim in size. The other preparations are—TINCTURA OPII, U. S., or Laudanum (one hundred and twenty drops to the fluidrachm); VINUM OPII, U. S., or Sydenham's Laudanum (formerly ʒi to f℥i); ACETUM OPII, U. S., or Black Drop (formerly gr. lxxv to f℥i).

MORPHINA.* U. S.

This alkaloid occurs in minute, colorless, shining crystals, according to Guy melting at 330° F. and subliming at 340° F.; insoluble in cold and nearly so in boiling water; only slightly soluble in cold alcohol and ether; freely soluble in boiling alcohol and in the fixed and volatile oils.

The Morphine Acetate (MORPHINÆ ACETAS), Sulphate (MORPHINÆ SULPHAS), and Hydrochlorate (MURIATE OF MORPHINE, MORPHINÆ HYDROCHLORAS) are all official. The first is a white powder; the last two occur snow-white in feathery crystals. They are soluble in water, of a bitter taste, and physiologically and therapeutically equivalent.

THERAPEUTICS.—The salts of morphine differ in their therapeutic value from opium chiefly in that they act with less power as sudorifics and in checking secretion in the bowels, and consequently are less constipating. The smallness of their dose and their perfect solubility fit them for hypodermic use. Almost the only purpose for which they are used in this way is to relieve pain. The advantages of the method are the quickness of the results and the increased power of relieving suffering which the remedy seems to acquire. In cases of severe pain hypodermics are invaluable; but it must be borne in mind that sometimes they cause most unpleasant symptoms. We have seen very alarming results from the injection of one-sixth of a grain, which dose is said to have caused death. In females, unless very robust, the maximum dose should be one-eighth of a grain (0.008 Gm.); in men, one-sixth to one-quarter (0.01–0.016 Gm.). The dose of a salt of morphine corresponding to a grain of opium is one-quarter of a grain.

There are several derivatives of morphine which have been recently brought forward as substitutes for that alkaloid.

PERONINE, morphine benzyl-ester hydrochloride, is a bitter, odorless, white, crystalline powder, slightly soluble in water, whose physio-

* For a very interesting paper upon the derivatives of morphine and their physiological effects, by D. B. Dott and Ralph Stockman, see *Proceed. Royal Soc. Edinb.*, 1890.

logical action has been studied by Mayor,[1] who finds that it produces in rabbits a condition of quiet with exaggerated reflexes, followed when the dose has been sufficient by violent convulsions, ending in death by asphyxia. It is asserted by Schröder[2] that peronine is intermediate in therapeutic powers between morphine and codeine, having both analgesic and hypnotic properties. Mayor states as a result of his experiments that its influence in depressing the sensibility of the pulmonic mucous membrane is very great. According to present evidence, its chief value in practical medicine is to allay respiratory irritation and quiet cough. Dose, from one-third of a grain to one grain (0.02–0.06 Gm.).

DIONINE, mono-ethyl-ester of morphine hydrochloride, is a white crystalline powder, soluble in seven parts of water. Concerning its physiological action we have almost no definite knowledge, but it is alleged to be somewhat hypnotic, very inferior to morphine as an analgesic, useful in the quieting of cough, and having some power of checking *night-sweats*. It is given in the doses of from one-sixth to one-quarter of a grain (0.010–0.016 Gm.). J. Heinrich[1] states that dionine affords a very useful method of curing the morphine habit, it relieving the symptoms when substituted for morphine in about one-third larger dose than the morphine, without producing the peculiar exhilaration which is the basis of the craving of morphine.

HEROINE, the diacetic ester of morphine, which occurs as a colorless, odorless, bitterish crystalline powder, is nearly insoluble in water, but forms a hydrochlorate which is freely soluble both in water and in alcohol. According to Dreser,[1] it produces in the lower animals stupor with convulsions, and has very little influence upon the circulation. On the other hand, it is a respiratory poison, lessening the amount of air moved, and diminishing the sensitiveness of the respiratory centres to an excess of carbonic acid in the blood. Its analgesic and hypnotic influences are affirmed to be very slight. Espinosa de los Monteros has reported a case of an asthmatic in which one-quarter of a grain* produced violent cyanosis, complete amaurosis, a very feeble pulse of 40, convulsive movements in the lower extremities, a fall of temperature to 96.6° F. in the axilla, and semi-coma ending in recovery.

Erich Harnack[2] affirms that it influences the heart more powerfully than morphine. We have used it with great satisfaction for the purpose of quieting cough; and in a case of frightful dyspnœa from pressure by a thoracic aneurism on the bronchial tubes it gave extraordinary relief. It usually produces no disagreeable symptoms, though occasionally headache and vomiting have been caused by it; and, according to personal reports to us, double vision may result from its use. The dose is one-

* The dose given was probably much larger than stated. See editorial in the *Medical Press* of September 29, 1899.

tenth to one-third of a grain (0.007–0.023 Gm.). The hydrochlorate may be used hypodermically.

CODEINA. U.S.

According to the statements of various observers, codeine produces in the lower animals symptoms very similar to those caused by morphine, —namely, in the frog, heightened reflexes, tetanic cramp with convulsions, also coma ; in the pigeon, restlessness, disturbances of respiration, violent convulsions ; in the dog, disturbances of respiration, languor, convulsive twitchings, also sleep. For detailed discussion of the observations of various investigators, see tenth edition of this work.

In man codeine is a very uncertain and feeble hypnotic, whose action, especially after large doses, is sometimes attended by marked restlessness. The statements of various clinicians as to its effects and practical value vary very greatly, the variance probably depending largely upon the quality of the codeine used, in many cases the drug exhibited having in all probability been contaminated with morphine. In S. Weir Mitchell's[1] experiments upon himself five grains produced no symptoms except slight increase in the pulse-rate, nausea, some giddiness, and a sense of heaviness about the head ; results which are in accord with the earlier experiments of Harley. Contrariwise, A. S. Myrtle[2] records a case of severe poisoning caused by four grains of codeine. There was first vascular excitement and exhilaration, then depression with great anxiety, nausea and vomiting, pale, cool, clammy skin, slight contraction of pupil, and sleeplessness, with slight delirium. Two cases of serious poisoning by eight grains have been reported.*

In our experience codeine has proved to be a practically useless remedy except in doses of half a grain for the purpose of controlling *bronchial irritation* in phthisis and other diseases. The dose of the alkaloid may be set down as from half a grain to two grains (0.03–0.13 Gm.), but in the administration of the larger amount the practitioner should be sure he has a preparation that does not contain morphine.

In former editions of this treatise the non-official opium alkaloids narcéine, narcotine, thebaine, papaverine, laudanine, porphyroxine, anarcotine, and cryptopine were discussed at length, but, as they have failed entirely to come into use as therapeutic agents, their consideration is here omitted : a full summary of our knowledge of their physiological action may be found in the tenth edition of this work.

HYOSCINÆ HYDROBROMAS—HYOSCINE HYDROBROMATE. U.S.

The U. S. Pharmacopœia defines hyoscine hydrobromate as the hydrobromate of an alkaloid obtained from hyoscyamus. The hyoscyamus plant is a member of a group of closely allied solanaceous plants which are capable of producing violent poisonings, which have more or less close

* See *Brit. Med. Journ.*, 1888, ii., and *New York Med. Record*, 1893, xliv.

conformity of symptoms, and concerning the nature and relation of whose active principles there has been much discussion and still remains some doubt. The important members of the group are the *Atropa belladonna*, *Hyoscyamus niger*, *Datura stramonium*, and *Duboisia myoporoides*. From these plants have been separated by various chemists a number of so-called alkaloids, but, according to the researches of Ladenburg (1879–1884), there are but three alkaloids having one formula and differing, therefore, in their molecular structure only. These alkaloids are *atropine*, *hyoscyamine*, and *hyoscine*. Subsequent to the researches of Ladenburg, another solanaceous plant, the *Scopolia carniolica*, came largely into commerce as the source of an alkaloid, *Scopolamine* or *Scopoleine*, which belongs to the atropine group.

Atropine and hyoscyamine have been obtained in crystalline form, whereas hyoscine is known only as a syrupy liquid, and is affirmed by chemists of repute not to have the formula assigned to it by Ladenburg. Before the general recognition of hyoscine as a distinct alkaloid, the dark syrupy liquid known in commerce as amorphous hyoscyamine was largely composed of hyoscine, and the hyoscine of earlier commerce was obtained from this body. It is now commonly affirmed that the commercial hyoscine is scopolamine, the British Pharmacopœia declaring hyoscine to be obtained from Scopola, and the Committee of Revision of the German Pharmacopœia recommending the change of the official title of "Hyoscinum Hydrobromium" to "Scopolamium Hydrobromium."

The correctness of these official declarations is, however, doubtful in view of the researches of O. Hesse, who believes that he has demonstrated that scopolamine is composed of two bases, hyoscine and atroscine, and has been in a measure confirmed by the studies of Louis Merck, who had the advantage of using enormous quantities of the base.* The matter is of importance in view of the different results which have been obtained by different observers in the use of hoyscine.

The physiological and therapeutic studies originally made by H. C. Wood were made with Merck's hyoscine, and a long continuing experience with the drug has shown that it yields a uniform result at the bedside. Concerning this hyoscine, Merck & Co. write, "Merck's hyoscine and its salts always have been and still are obtained from hyoscyamus." The scopolamine of Merck's trade catalogue is the alkaloid obtained from *Scopolia atropoides*. The practitioner who uses hyoscine should see that the alkaloid he administers is obtained from the hyoscyamus plant.

Hyoscine hydrobromate occurs in minute, colorless, rhombic crystals, which are freely soluble in water and in alcohol.

The symptoms which are produced in man by decided doses of hyoscine are dryness of the mouth, flushing of the face, great sleepiness, associated in some cases with semi-delirious mutterings, and a feeling of giddiness like that of intoxication. The respirations are lessened in frequency and the pulse-rate is usually somewhat diminished ;† mydriasis is usually, but not always, pronounced. After very large doses the symp-

* Society of Chemical Industry, June, 1897.

† It has been noted a little accelerated. (Case, *Therap. Gaz.*, 1889, J. S. Gibb.)

toms mentioned are more intense ; the pulse becomes slow and full, but, according to the sphygmographic tracings of J. B. Andrews, without alteration of tension, the pupils dilated, the mouth and throat excessively dry, and the voice hoarse or even partially suppressed, probably from paralysis of the vocal cords. The respirations are slow and full, and are said by H. M. Wetherill to be sometimes Cheyne-Stokes. The face and the general surface of the body are suffused, muscular relaxation is pronounced, and loss of coördination usually very evident. The skin, so far from being abnormally dry, is commonly bathed in perspiration. Several observers assert also that there is a rise of temperature. Sometimes the delirium is active, accompanied by visual hallucinations, and clonic convulsions with opisthotonos have been noted. Mairet and Combemale found that monkeys when poisoned by it gave evidences of the presence of hallucinations, such as are sometimes produced in man.*

* The fact that numerous observers had asserted that the impure amorphous hyoscyamine of commerce was more powerful than the pure crystallized alkaloid led H. C. Wood, in 1884, to a physiological and therapeutic study of hyoscine, which led to the use of the remedy in practical medicine. The statements of the text are the results of these researches. Partial physiological studies of the alkaloid have since been made by Gley, Rondeau, Mairet and Combemale (*Compt.-Rend. Soc. Biolog.*, 1887), A. Sohrt (*Inaug. Diss.*, Dorpat, 1886), Claussens (*Inaug. Diss.*, 1883), and Kobert (*Archiv f. Exper. Path. Pharm.*, 1887), the paper by Kobert being apparently a restatement of the work done by his pupil Sohrt. In some respects these researches confirm the results obtained by H. C. Wood, but in other points they differ so widely from his results, as well as among themselves, that it is practically certain that different experimenters have worked with different alkaloids or combinations of alkaloids, resulting in a confusion which can scarcely be converted into order by discussion. For these reasons we have left the text as it has been in the former editions of this book, and will consider in the present foot-note the important matters in the subsequent literature. The experiments of H. C. Wood were made with hyoscine obtained from Merck.

One of the most important differences between the results of H. C. Wood and those of subsequent investigators is in regard to the pneumogastric nerve. Claussens, in agreement with H. C. Wood, found that these nerves are not paralyzed by the alkaloid, but Rondeau, Sohrt, and Kobert affirm that large doses tend to produce such paralysis, Kobert stating that when hyoscine is placed directly upon the heart of the frog which has suffered diastolic arrest from muscarine systolic contractions are re-established, and also that when it is applied to the exposed heart of the frog it prevents the production of diastolic arrest by galvanization of the vagus centre. In further experimentation upon dogs and cats, it was found that when the vagus with its accompanying nerves was cut galvanization of the central end caused no sinking of the blood-pressure if hyoscine had been previously administered, and Kobert deduces from this that hyoscine paralyzes the vagus nerve. The experiment evidently proves no more than that under the influence of hyoscine the depressor nerve is no longer able to cause vaso-motor dilatation. It is possible that directly applied to the frog's heart hyoscine may paralyze the vagi, and yet its influence upon those nerves be so slight as not to be apparent when the alkaloid has been absorbed and is acting upon the whole organism. Almost all clinical observers have noted that the pulse becomes slower rather than more rapid under the influence of hyoscine, and this assuredly shows, too, that the drug has no marked paralytic action upon the vagus, for the pulse of vagus-paralysis is of necessity very rapid. It is possible to explain Kobert's results by the supposition that the hyoscine he used contained some atropine. Kobert also found that hyoscine has no influence upon the spinal cord of the frog when given in doses of one-five-hundredth part of its weight; but, as the paralyzing influence of the alkaloid in H. C. Wood's experiments was marked with the one-thousandth part of the frog's weight, while one-five-hundredth part caused complete loss of reflex activity with absolute paralysis, and death from respiratory paralysis, it is evident that Kobert, or rather his pupil, Sohrt, had a drug essentially different from that used by H. C. Wood.

In the studies of H. C. Wood[2] hyoscine caused in the frog a general motor and reflex paralysis, progressively increasing until death from failure of respiration. When recovery occurred there was no stage of tetanus following the palsy. Neither the muscles nor the motor nerves were sensibly affected, and the paralysis was dependent upon depression of the motor centres of the spinal cord. No evidence could be obtained of affection of the sensory side of the nervous system. In mammals, the symptoms produced were loss of muscular power, disturbance of respiration, and marked tendency to stupor, with finally death by asphyxia. The alkaloid had very little effect upon the circulation, though after enormous doses when life was maintained by artificial respiration the vaso-motor system was finally paralyzed. On the heart itself hyoscine acted as a very feeble depressant; it did not paralyze the pneumogastrics. It is evident that in man, as in animals, the motor tract of the spinal cord and the cerebral cortex are depressed by this alkaloid, which is also a respiratory paralyzant.

Upon the pupil hyoscine acts like atropine, a half of one per cent. solution rapidly paralyzing accommodation and dilating the pupil. It is said that it does not produce any irritation, and that its maximum effects are reached in one-third the time necessary for those of atropine, and are more permanent and less affected by eserine.* MM. E. Gley and P. Rondeau[3] have found that the mydriasis is not prevented by previous destruction of the cervical sympathetic in the rabbit, and that irritation of the sympathetic nerve will increase the dilatation.

SUMMARY.—The dominant physiological action of hyoscine is upon the cerebral cortex, producing sleep often accompanied by a low delirium. It is also a centric depressant of respiration, and depresses, though somewhat feebly, the whole motor cord: upon the sexual centres it acts more powerfully. Its influence upon the circulation is very slight, and it appears to exert no distinct influence on the nerves or muscles. On the mucous membrane and probably on the muscles of the throat it acts powerfully, suppressing secretion and interfering with function.

THERAPEUTICS.—Hyoscine is a valuable hypnotic in those forms of insomnia in which sleep is banished by a continual flow of thoughts or mental images passing through an excited brain; hence it is often very effective in the insomnia of *delirium*, of *acute mania*, or of other forms of *insanity*. In some cases of insanity with cerebral excitement most excellent results are produced by the administration every three to five hours of small doses that will calm without causing sleep. As an hypnotic the alkaloid lends itself very well to combinations, intensifying greatly the influence of morphine, chloral, trional, and other drugs of the class. In cases of severe kidney disease it would seem to be a

* John Tweedy, *Lancet*, Dec. 1886.

safer hypnotic than is morphine, and as it has no sedative influence upon the heart, it may be used when the feeble condition of that viscus forbids chloral.

The use of enormous doses (grain one-fiftieth to one-twentieth) of hyoscine as a curative remedy in *acute insanity* has been advocated by H. R. Costons, and a remarkable case is recorded by Balagopal,[4] in which one-sixth of a grain was given hypodermically to a patient suffering from violent, *acute mania*. Immediately after the injection the patient fell, crying that he was dying; his face became deadly pale, the conjunctiva insensitive, the breathing difficult and stertorous, the limbs spasmodically contracted. After recovery, which occurred without remedies other than hypodermic injections of ether, the patient's mental condition rapidly improved, and in a week he was well.

Probably through its influence upon the spinal centres hyoscine is useful in all cases of *sexual excitement*, such as *nymphomania*, *spermatorrhœa*, and allied affections. It is the most certain remedy that we have in ordinary cases of over-frequent *seminal emissions*, which can usually be controlled by the administration of the one-hundred-and-twentieth to one-eightieth of a grain on going to bed.

As an analgesic hyoscine is of little value, though Winnett[5] states that it is very serviceable in the crises of *locomotor ataxia*. It has been used to a considerable extent in certain spasmodic disorders. Edlesen, as early as 1881, affirmed its value in *asthma* and *whooping-cough*. Erb has used it with advantage in various spasms. In *spinal accessory spasm* it has in our hands failed. On the other hand, in pronounced *paralysis agitans*, attended by much aching pain, we have seen it give very great relief from both pain and tremors. Usually in these cases it should be administered only at bedtime, as it is merely a palliative, and if used continually is prone to lose its power.

Toxicology.—No fatal case of poisoning by hyoscine is on record. H. A. Hutchinson[6] took a quarter of a grain of very impure hyoscine: quiet coma with entire muscular relaxation was produced, and lasted eleven hours. The fiftieth of a grain has, however, several times caused very alarming symptoms, and much smaller doses are affirmed to have produced serious effects (see Carey[7]).

O'Hara[8] saw one-ninety-sixth of a grain administered hypodermically produce very severe disturbance, lasting for twenty-eight hours, with total lack of remembrance of occurrences which took place during the seven hours following the injection; while Root[9] asserts that one-three-hundredth of a grain given by the mouth produced violent poisoning, and even one-twelve-hundredth very pronounced symptoms. The dispensing of these exceedingly minute quantities of a drug requires so much care that it is extremely probable that more of the alkaloid was given than is alleged.

Administration.—Hyoscine very rarely if ever causes other disagreeable after-effects than dryness of the throat, although occasionally some headache has been noted. Nausea, constipation, or other disturb-

ance of the alimentary canal is never produced. The action of hyoscine given hypodermically is manifested inside of ten minutes, and lasts from about six to eight hours. In severe excitement, especially that of violent insanity, the dose should be repeated every six or eight hours. The remedy being free from irritant properties, no local ill effects follow its hypodermic administration. The dose for hypodermic use is from the one-hundred-and-fiftieth to one-eightieth of a grain (0.6–0.8 milligramme). Excessive susceptibility to the action of hyoscine being a not infrequent idiosyncrasy, it is best to give at first amounts below the minimum dose here stated. The tastelessness of hyoscine makes it exceedingly easy to administer to insane or other patients without their knowledge.

Owing to its great influence upon the throat, hyoscine is strongly contra-indicated in cases of acute disease of the throat sufficiently violent to interfere with deglutition or respiration. Thus, we have seen it, when given in violent *anginose scarlatina* with delirium, cause such rapid increase in the difficulty of respiration as to suggest that it played an important *rôle* in the production of the fatal asphyxia.

CHLORETONE.

Chloretone, *Acetonchloroform*, or *Trichlor Tertiary Butyl Alcohol*, is a white crystalline compound with a camphoraceous odor; very soluble in strong alcohol and ether, soluble to the extent of about one per cent. in cold, more soluble in boiling, water.*

Acetone-chloroform was first made synthetically by the German chemist Willgerodt, in 1881. In September, 1884, he described a few experiments with it, and suggested that it might possibly be used like chloral.

Without knowledge of these experiments, in 1891 John J. Abel began to experiment with it, and in 1894 detailed its value and described its usefulness as a practical hypnotic and anæsthetic for the physiologist before the American Physiological Society (see *Science*, January, 1895).

Physiological Action.—The moderate dose produces in the dog a profound sleep, with complete anæsthesia which lasts for several hours. During this period the respiration is not distinctly affected and the blood-pressure remains about normal. After a very large dose the animal may remain anæsthetic as long as four days, and wake without harm; but if the dose be sufficient, after several days of sleep death occurs from asphyxia. In the experiments of E. M. Houghton and T. B. Aldrich,[1] its aqueous solution applied to the bared frog's heart slowed the rate and produced more complete contraction of the organ, whilst the blood-pressure in dogs after six hours of complete anæsthesia was the same or a little higher than at the beginning. It is stated also that it has

* Abel states that Faust has found that urethan and chloretone rubbed together make a fluid. The physiological properties of this substance do not seem to have been investigated.

no action upon the blood itself. It has a very marked effect upon the sensory nerves, so that it may be used with great success as a local anæsthetic.

Having failed even after the largest doses to find it, or acetone, or chloroform in the urine or expired air, and having obtained evidence that its employment increases the chlorides in the urine, Houghton and Aldrich have reached the conclusion that it is probably decomposed in the body.

THERAPEUTICS.—Chloretone has been used in practical medicine to some extent, but apparently with such timidity that little satisfaction has been obtained except from its employment as a local anæsthetic. Its one per cent. solution is distinctly germicidal, and may be used as an anæsthetic to *irritable ulcers* and *infected wounds*, also probably as a local anæsthetic in minor surgery.

The dose has been stated to be from two to ten grains, but we have given thirty grains in twelve hours without the production of any distinct symptoms. W. M. Donald[2] has reported a case in which one hundred and twenty grains were taken during twenty-four hours; the result was a profound sleep lasting for six days, without any untoward symptoms except gastric irritability. During the latter part of this period the patient could be aroused for brief conversation; the pulse ranged from 85 to 104, bodily temperature fell to 97.60° F., and, though some food was taken, there was much irritability of the stomach.

In gastric irritation chloretone is said to act happily in doses of from eight to ten grains. In the physiological laboratory chloretone is a very useful anæsthetic: 0.2 Gm. per kilo body-weight may be given when it is intended to keep the animal alive. If recovery is not desired, much larger doses may be administered, in many cases without interfering with the experiment.

CHLORAL. U. S.—CHLORAL HYDRATE. U. S.

Chloral, which is itself not used in medicine, is an oily liquid which at the ordinary temperature gives off pungent fumes, and which is manufactured by the action of chlorine on alcohol; by union with water, it is converted into a hydrate.

Chloral Hydrate, or *Chloral* of the U. S. Pharmacopœia, is a volatile, crystalline solid, of a hot, burning taste, insoluble in cold chloroform, but very soluble in water, ether, and alcohol. It usually occurs as transparent, colorless tablets, but sometimes in acicular or even in rhomboidal crystals.

If an alkali be added to a solution of chloral hydrate, it breaks up into formic acid and chloroform, which latter, when water has been the solvent, at once separates in the form of oily drops.

Local Action.—Chloral is distinctly germicidal and antiseptic, and was at one time used to some extent for preserving cadavers, keeping urinals pure, and allied purposes. As shown by Keen,[1] a solution of

twenty to forty grains to the ounce will preserve animal tissues almost indefinitely without interfering with their microscopic structure. It is also somewhat irritant in its action, and after a time sedative to the sensory nerves, and, it may be, to all tissues.

Absorption and Elimination.—Chloral is absorbed with great rapidity, its action being often manifested within five minutes after its ingestion. It circulates through the body as chloral ; its exact fate in the system has not been determined, but it probably escapes from the body in part unchanged and in part in the form of compounds. It was recognized in the urine by A. Tomascewicz[2] by means of the delicate isocyanphenol reaction * of Hoffmann. Feltz and Ritter[3] believed that they had found sugar in the urine of chloralized animals, but Von Mering and Musculus and F. Echard[4] have shown that the substance which reduces the copper solution will not undergo fermentation, and Von Mering and Musculus have separated it, as *urochloralic acid*, in colorless, shining needles, often arranged in star-like groups, soluble in water and in alcohol, insoluble in ether. The existence of this acid has been confirmed and its chemical properties studied by A. Borntraeger[5] and by E. Külz,[6] who found it to be physiologically inert.

Physiological Action.—*General Action.*—When chloral is given to man or other mammals in moderate doses, the most prominent result in the great majority of instances is a quiet sleep, as closely allied as possible to natural sleep. The subject can readily be aroused from the lighter degrees of this, waking to full consciousness, but soon dropping off again when left quiet. The pulse is in this degree of action not affected, or is rendered a little slower ; the pupil is contracted, but becomes normal so soon as the subject is awakened ; the respiration is deep, full, and regular. When larger amounts are given, the sleep is much deeper, and may pass into profound coma ; the respirations fall in number ; the pulse is weakened and rendered slower, but may become rapid and irregular if the dose has been toxic ; the temperature is reduced ; the muscular system is relaxed, and both sensibility and reflex action are diminished. If a fatal dose has been taken, all these symptoms are intensified : with coma, intense muscular relaxation, weak, thready pulse, and a pupil contracted at first, but afterwards dilated, the victim gradually sinks into death, paralyzed and anæsthetic. The immediate cause of death is usually a centric paralytic arrest of respiration ; but in many cases there appears to be a simultaneous arrest of the cardiac action, and it is probable that fatal syncope may at times occur. At the post-mortem examination, congestion of the meninges and substance of the brain and cord, and of the lungs, is commonly found. The blood is thought by Richardson[7] to coagulate less firmly than when normal.

The most constant and prominent of all the symptoms produced by

* Many chemists have failed to find chloral for want of a delicate test. F. Ogston (*Edinb. Med. and Surg. Journ.*, xxiv. 292) affirms that ammonium sulphide affords a means of recognizing minute amounts of the drug.

moderate doses of chloral is sleep : this is without doubt due to a direct action of the drug upon the cerebrum. In most cases, as already stated, it is quiet, but sometimes it is restless, and in man has occasionally even been wildly delirious, although it is somewhat uncertain whether the latter condition may not have been due to impurities in the drug. It seems to be well established that in the milder degrees of this sleep there is no anæsthesia. We have seen the hyperæsthesia * spoken of by Demarquay[8] after small doses of chloral, and there can be no doubt that it is an occasional, if not a constant, phenomenon. Rajewsky[9] states that there is in frogs a corresponding period of over-excitability of the reflex centres, and that in rabbits he has noticed a glowing heat borne without much complaint, when pinching would produce violent outcries. In *very large* doses chloral produces anæsthesia ; but, unless the amount employed be so great as to be toxic, this anæsthesia is in most cases very trifling.

Motor System.—The paralysis and loss of reflex excitability induced by chloral are not muscular in their origin, for Labbée has found that after death the muscles respond perfectly to galvanism. Both Labbée and Rajewsky have found that the motor nerves are in no wise affected by large or even fatal doses of chloral, which must therefore act upon the spinal cord to produce the paralytic phenomena. The experiments of Rajewsky have afforded positive confirmation of the conclusion arrived at by this process of exclusion ; for he found that in the latter stages of chloral-poisoning direct irritation of the spinal cord gave rise to much less severe spasms than in the unpoisoned animal. Before this paralytic stage is reached, as already stated, Rajewsky affirms that in the frog there is a period of increased reflex activity, and that at this time stimulation of the spinal ganglia shows that they are more susceptible than normal. The observer last named states that these phenomena occur just as freely after destruction of Setschenow's centre in the frog as before, and are therefore independent of it.

Circulation.—According to Demarquay, when chloral has been administered to animals there is evident enlargement and engorgement of all their blood-vessels ; and Rajewsky states that he has found sinking of the blood-pressure in rabbits caused by small as well as large doses of the drug. On the other side, Labbée[10] asserts that the rabbit's ear grows pale after the injection of a very feeble dose. In man, Bouchut has obtained sphygmographic traces which he thinks indicate a primary increased arterial tension. Nancias, of Venice, has found the tension normal, but Anstie and Andrews[11] confirm the results of Bouchut when small doses are employed. Preisendorfer,[12] in a series of sphygmographic studies, thought that there might be a brief primary rise of arterial press-

* Bouchut (*New York Med. Gazette*, Dec. 1870), Dieulafoy and Krishaber (*Amer. Journ. Med. Sci.*, Jan. 1870), Giovanni and Ranzoli (*Schmidt's Jahrbücher*, cli.), and Rajewsky (*Ibid.*) confirm this, while Liebreich and Labbée deny it; Hammarsten, who has noticed such hyperæsthesia, is inclined to think it apparent rather than real.

ure in man, as in animals, but under the full action of chloral the arterial pressure steadily sinks. We do not think that much confidence is to be attached to the clinical observations of Bouchut and of Anstie and Andrews, since the sphygmograph seems to be an entirely unreliable instrument when used for the comparative study of arterial pressure ; and in confirmation of the statements of Rajewsky, David Cerna has found in our own laboratory that it is not possible in curarized animals to elevate arterial pressure with any dose of chloral, so that if any rise of pressure (as seems improbable) is ever produced in the normal man or animal by chloral, such rise must be indirect and, probably, due to respiratory disturbance. Very large doses, according to both Andrews and Da Costa,[13] decidedly lessen arterial pressure. The characteristic influence of therapeutic, and still more of toxic, doses is to produce a fall in the blood-pressure, usually accompanied by a lessening in the frequency of the heart's action, which Cerna believes to be largely due to an influence upon the cardio-inhibitory centres ; although Rajewsky affirms that the slowing of the pulse in the frog and in the rabbit is produced after section of the inhibitory nerves, and is therefore independent of them. The fall of blood-pressure is probably owing in part to the vaso-motor paralysis, but perhaps in largest part to depression of the heart. The vaso-motor palsy is probably chiefly caused by an action upon the dominant centre, but Kobert[14] has shown that there is also, after a very large dose of the chloral, palsy of the coats of the vessels. When toxic doses have been employed, the heart, after numerous pauses, is finally arrested in diastole. Analogy indicates very strongly that this arrest is due to a direct influence upon the heart-muscle or ganglia, and the researches of Sidney Ringer and H. Sainsbury[15] and of David Cerna[16] seem to demonstrate (the contrary results obtained by Labbée notwithstanding) that when chloral is brought in direct contact with the isolated heart of the frog there is an immediate and persistent loss of power, ending finally in diastolic arrest.

In poisoning in man, the pulse has towards the last been very feeble, generally rapid and irregular, and even in some cases in which recovery has occurred it has been altogether absent for a time. The experiments of Ringer and Sainsbury are so concordant with this that it appears to be established that chloral is a *direct depressant to the heart*, which is capable of suddenly and unexpectedly destroying life, precisely as does chloroform.

Respiration.—In full doses, chloral lessens the number of respirations per minute, causing them to become slow and full ; when toxic doses are taken this action becomes more and more marked, the rhythm is much affected, and the respiration grows markedly irregular, and sometimes very rapid and shallow, until it ceases. As these phenomena occur equally after section of the vagi (Rajewsky), the influence of chloral must be exerted upon the respiratory centre at the base of the brain.

Tissue Change.—Charles Richet[17] has found that toxic doses of chloral reduce very greatly the elimination of carbonic acid, at the same time that they lower the bodily temperature. So far as large doses are

concerned, A. Gritzka[18] is in accord with this, although he asserts that small doses increase carbonic acid elimination. It is plain that the profound muscular quiet produced by chloral must lead to lessened oxidation. Julius Peiser[19] affirms that chloral increases the degeneration of albuminous tissues.

Temperature.—A most remarkable action of chloral is upon the temperature: in this point all observers are in accord with Richardson, of London, who has seen the temperature fall 6° F. in a rabbit which recovered. Bouchut has noticed a fall of 2° (C.?) in an infant, and Da Costa and other observers have noticed slighter reductions of temperature in man after therapeutic doses. In a case reported by Levinstein,[20] after six drachms of chloral the temperature rose to 39.5° C. (102.1° F.), and subsequently fell to 32.9° C. (91.22° F.). Hammarsten has found that the fall of temperature is very rapid, 6° C. in an hour, and that it occurs in animals well wrapped up and laid in a warm place.

SUMMARY.—Upon the cerebrum chloral acts as a powerful hypnotic; in full doses it acts as a depressant upon the centres at the base of the brain and upon the spinal cord: it causes slowing and weakness of the heart's action, and probably vaso-motor paralysis, also centric slowing of the respiration, with loss of reflex activity, muscular weakness, and some anæsthesia, all of spinal origin; in fatal doses it usually produces a gradual death by paralyzing the respiratory centres in the medulla, although in rare cases it kills suddenly by directly paralyzing the heart, which always stops in diastole. Its action in very small doses is uncertain, but there is some evidence to indicate that it irritates or stimulates the spinal and the cardiac centres. On the vagi and on the motor nerve-trunks it has no marked influence. It does not undergo the chloroformic decomposition by the alkali of the blood or in the system, and is eliminated as uro-chloralic acid.

Action as Chloral.—Liebreich[21] was led to the discovery of the value of chloral as a practical medicine by the knowledge of the fact that it is converted when in solution by alkalies into chloroform and formic acid, and the expectation that chloroform would be generated by the alkalinity of the blood. This theory, which at one time held, has been so completely disproved as almost to have been lost sight of. A discussion of it may be found in full in the tenth edition of this treatise. Suffice it for the present to say that it is proved that chloral circulates in the blood as chloral, that no conversion of it takes place in the body into chloroform, and that the symptoms which it produces are distinct from those caused by chloroform; chloral producing a much longer and more intense sleep than does the proportionate dose of chloroform, but having a very much feebler anæsthetic influence; and further, that in the "salt frog," with a circulating fluid completely neutral, chloral acts precisely as in the normal frog (Rajewsky).

THERAPEUTICS.—The results of the clinical use of chloral are in strict accord with its known physiological action. The indication which

it most usefully meets is to *induce sleep.* The more purely nervous the wakefulness the more successful the remedy. When from functional over-excitement of the brain due to excessive mental strain, or from anxiety or other kindred cause, the patient cannot sleep, chloral is, probably, the most certain of the hypnotics. On the other hand, when severe pain causes wakefulness, chloral is of very little value,—at least in doses which we think safe. Sometimes even in these cases sleep will come, but it will very often be a restless, troubled sleep, with moaning or other indications of suffering ; and it may be that the patient on awaking will complain that he has suffered more while sleeping than when awake.

In the *sleeplessness* occurring at times during *convalescence* from acute disease, chloral is very efficacious. In the early stages of *fevers* it is sometimes of advantage ; Russell[22] recommends it especially in the *wild delirium of typhus* in its earlier stages. In advanced fever-cases, when the symptoms are gravely adynamic, we believe that the use of chloral would be very perilous. In *delirium tremens* it often induces sleep readily, but not rarely it fails, even in large dose. In the sleeplessness of acute puerperal or non-puerperal *mania* there is abundant testimony to the value of chloral. It must not be forgotten that chloral is a dangerous remedy when there is cardiac weakness ; and when in any of the diseases just spoken of there is reason to suspect a fatty or even a feeble heart, great care must be exercised in the administration of chloral. Under such circumstances the dose of fifteen grains should not be exceeded, and should not be repeated more than once unless after an interval of several hours.

The second indication to meet which chloral may be employed is *to relax spasm.* For this purpose it has been used with advantage in *puerperal* and *uræmic convulsions.* It must be remembered that in many of these cases, although next to chloroform the best palliative, it is only a palliative, and must be used merely to quiet the nervous disturbance until other remedies can have time to act. In *tetanus* it has been affirmed that chloral is *the* remedy. Joseph R. Beck[23] has collected, of the traumatic form of the disease, thirty-six cases, with twenty-one recoveries, in which chloral constituted the whole or the major part of the treatment. References * are given below to fifty-six cases in addition ; so that the

* RECOVERY.—Fergusson (*Edin. Med. Journ.*, July, 1871) ; Watson (*Lancet*, 1870) ; Bartlett ; May ; Ballantyne ; Cushing (*Pacific Med. and Surg. Journ.*) ; Lovegrove (*Brit. Med. Journ.*, 1872, 493) ; Herndon (*Atlanta Med. and Surg. Journ.*, 1873, 69) ; Macnamara (*Indian Med. Gaz.*, April, 1871) ; Richelot (*Bulletin Thérap.*, lxxxvi.) ; Lucian Papillaud (*Gaz. Médicale*, 1875, 176) ; Bourdy (*Bull. Thérap.*, lxxxvi.) ; Cane (*Lancet*, 1876. i. 564) ; Cauvy (*Bull. Thérap.*, xciii. 186) ; Durand (*Centralbl. f. Chirurgie*, 1876, 778) ; Laurens (*Le Progrès Méd.*, 1876, 180) ; Puglièse (*Journ. de Thérap.*, 1875, 244) : each one case ; Cargile (*Lancet*, 1877, ii. 158), three cases ; Boon (*London Pract.*, xx. 161), two cases ; Roberts (*Amer. Journ. Med. Sci.*, lxxiv. 420), three cases ; Garnett (*Cincinnati Lancet and Clinic*, 1880, 316), two cases.

FATAL.—Porta (*Schmidt's Jahrbücher*, cli. 110), two cases ; Macnamara (*Indian Med. Gaz.*, April, 1871), six cases ; Baudon (*Bulletin Thérap.*, lxxxvi.), three cases ; Blin (*Ibid.*), three cases ; Petit (*Centralbl. f. Chir.*, 1876, 792), three cases ; Roberts (*Amer. Journ. Med. Sci.*, lxxiv. 420), three cases ; Cruveilhier (intravenous) (*Bulletin Thérap.*,

figures stand forty-eight recoveries and forty-four deaths. These results do not seem to warrant the high estimate which has been set upon the value of chloral in tetanus. Very extraordinary results have been obtained by Macnamara[24] in tetanus by using chloral simply at bedtime (forty grains), with an occasional dose (thirty grains) in the morning when there is high temperature; and administering brandy, milk, and eggs very freely during the day. Chloral is undoubtedly a valuable remedy in tetanus and in strychnine-poisoning; there is, however, no reason for relying upon its exclusive use.*

In *trismus nascentium*, as originally recommended by Widenhofer,[25] it is undoubtedly very valuable. Widenhofer gave it to the young babe in one- and two-grain doses by the mouth, or, when the spasms prevented, in double the quantity by the rectum. In *chorea* it is not directly curative, but is of great importance when it is essential to temporarily check the violence of the movements. As a nocturnal quietant and hypnotic, it is of the highest value in cases of *acute chorea* in which speedy death is threatened from the incessant and violent movements; also in cases complicated with fractures, where a temporary lull is of importance. In *puerperal convulsions* its use in large doses has met with a great deal of favor. A half-drachm may be exhibited at once, and half the quantity every hour or two *pro re nata*.

In the *convulsions* of children it has been employed with apparent good; in *cramps*, in *singultus*, in the spasmodic *nocturnal enuresis* of children, in *laryngismus stridulus* and other spasmodic affections of the glottis, in *nocturnal emissions*, in *whooping-cough*, and in all forms of severe spasmodic disorder when it is desired temporarily to suppress the motor disturbance, chloral remains the standard remedy. In *asthma* it has sometimes been of use, but more often it has failed. Its hypodermic use in the algid stage of *cholera*, as recommended by Dr. Hall,[26] appears to us of very doubtful value.

The third indication for which chloral has been used is to *relieve pain*. That it will do so when given in very large doses there can be no doubt; but, unless the dose be so large as to be dangerous, chloral is of little value as an analgesic. Its powers in this direction are incomparably less than those of opium, and its habitual use is attended by grave dangers.

As originally suggested by Lyon Playfair,[27] chloral is often used in the early stages of labor to lessen the severity of the pain; it is stated also to be often of great service as a relaxant when there is rigidity of the os. Fifteen grains may be administered and repeated in half an hour if necessary.

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lxxxvi.); Labbée (*Ibid.*); Itard (*Schmidt's Jahrb.*, cli.); Lannelongue (*Bulletin Thérap.*, 1874, lxxxvii.); Verneuil (*Ibid.*, 1874, lxxxvii.); Boon (*London Practitioner*, xx. 161); Boucquier (*Centralbl. f. Chir.*, 1876, 717); Bresson (*Le Progrès Méd.*, 1876, 180); Puglièse (*Journ de Thérap.*, 1875, 244): each one case.

* For a paper discussing the relations of chloral to various mostly unimportant alkaloids, see *Arch. f. Exper. Path. und Therap.*, ix. 440.

Locally a solution of chloral (ten per cent. to saturation) has been used with asserted very good effects as a stimulant and antiseptic in *foul ulcers*, *buboes*, *bedsores*, etc., especially when the discharge is free,—as a hæmostatic when there is oozing of blood,—and as an antiseptic and local anæsthetic in *uterine* and other *cancers*. Applied to the skin, it is a powerful irritant, and has been proposed as a vesicant, but is said to cause excessive pain.[28]

The intravenous injection of chloral, as suggested by Oré,[29] for the purposes of anæsthesia, and for the combating of *tetanic spasms*, is entirely unjustifiable and is at present rarely practised, death having in various cases resulted from the unexpected violence of its action or from the coagulation of the blood which it produced.

Toxicology.—The minimum fatal dose of chloral is hardly established, but thirty grains have produced death. (See *Administration.*) In very many cases, however, recovery has occurred after the taking of several drachms; indeed, Eshleman has reported recovery after the ingestion of four hundred and sixty grains. There are no pathognomonic lesions found after death from chloral, but a dark, bloated countenance and other evidences of death from asphyxia have been noted.

The treatment of chloral-poisoning is identical with that of opium-poisoning, consisting in the free use of internal and external stimulants, such as sinapisms, dry heat, frictions, flagellations, etc., to maintain the circulation, and of shaking, walking, application of the dry electric brush, cold douches, etc., to keep up the respiration. In practising these measures it must be remembered, however, that the patient in chloral-poisoning is much more apt to die of exhaustion, and especially of cardiac failure, than in opium-poisoning, and that therefore those methods of arousing the nerve-centres which do not, like walking, require the expenditure of effort on the part of the patient are to be preferred. Artificial respiration should always be resorted to before natural respiration altogether fails, and Clemens[30] has found that animals asphyxiated by chloral may often be at once aroused by the inhalation of oxygen. Atropine and strychnine are important remedies. B. W. Stone[31] reports recovery from four hundred and twenty-five grains of chloral after the hypodermic use of one-fifth of a grain of strychnine in divided doses. Digitalis may be given to sustain the heart. I. M. Booth[32] reports a case of recovery after about one hundred and ten grains of chloral under the use of tincture of belladonna. Lauder Brunton[33] has shown that if the bodily temperature be maintained artificially animals survive doses of chloral usually fatal, and in human chloral-poisoning the bodily warmth should be maintained by the use of dry external heat, hot blankets, hot baths, and other devices.

While some affections have been erroneously attributed to *chronic chloral-poisoning*, there seems to be no doubt that its long-continued use often does produce serious symptoms. The cases are divisible into two or three groups, which are, however, really artificial, as is shown by the occurrence of cases belonging to two or even three of the groups.

In the first group the respiration is chiefly affected. The dyspnœa may be slight, and may only be felt at times, as after exertion or after meals; but it may be constant and alarming. Cases of this character are reported by Jastrowitz, by Schule, and by Ludwig Kirn.[34] In one instance (N. R. Smith[35]), death from bronchial effusion is believed to have been caused by chloral. Kirn[36] affirms that in some cases mental disturbance with hallucinations occurs.

In the second group of cases, eruptions of the skin are the chief manifestations of the toxæmia. In the mildest of these there is no distinct rash, only the occasional appearance of transient red blotches on the face or neck. But a very extraordinary tendency exists towards the production of a rash or discoloration at the slightest cause, so that drinking a glass of wine will produce an intense, even livid, erythematous redness of the face. In other instances there is marked erythema (Schule[37]), occurring first in spots upon the face, but extending downward to the trunk, becoming more and more general, and showing a marked tendency to follow the nerve-trunks. This erythema is seemingly due to vaso-motor weakness, and consequently is allied to other more urgent symptoms seen in chloral toxæmia. Sometimes it invades the mucous membranes, which become red, swollen, and œdematous; and if the glands are involved, as in a case reported by Chapman,[38] the result may be serious. A deeper implication of the vaso-motor and cardiac nervous system was probably the cause of the general œdema, profound weakness, and failure of heart-action in the case recorded by N. R. Smith (*loc. cit.*), and possibly also of the desquamation of the cuticle and ulcerations about the nails noted in some of his cases by the same physician.

In the third group of cases, petechiæ, ecchymoses, ulcerations, and even high fever and other pyæmic symptoms, are asserted to have been produced by the continuous use of chloral. It seems to us, however, very doubtful whether the drug really was the cause of the sypmtoms which have been recorded by Crichton Brown, by Monkton, and by Kirn.

The habitual use of chloral as a narcotic has been indulged in, it is asserted, to a considerable extent, and George F. Elliott[39] reports symptoms like those of *delirium tremens* as following the withdrawal of the accustomed draughts.

Administration.—Although the continuous use of chloral may lead to a very serious chronic poisoning, we have no knowledge that the chloral itself accumulates largely in the system; and it certainly has no cumulative action like that of digitalis, in which a sudden outbreak of symptoms occurs without warning. On the other hand, the single large dose of chloral in rare cases acts with unexpected violence. It has frequently been given in doses of thirty grains. That this is not entirely safe, however, is shown by the case of Reynolds,[40] in which forty-five grains caused most alarming symptoms; by that of Watson,[41] in which eighty grains, given in ten-grain doses spread over thirty-six hours,

nearly proved fatal ; and especially by a number of cases recorded by H. W. Fuller,[42] in some of which very alarming symptoms followed the exhibition of thirty grains, and in one death in a healthy young woman of thirty. Schwaighofer,[43] of Vienna, records coma and death in a drunkard following the ingestion of half a drachm. W. H. Lathrop [44] details the case of a man previously healthy, but suffering from delirium tremens, who took sixty grains between 12 and 1 P.M., at 2.30 P.M. twenty grains more, and at 3 P.M., no effect being manifest, twenty grains more. His physicians then left him sleepless and complaining only of a slight paralysis of the lower extremities ; and almost in a moment he was dead. Other cases might be quoted,[45] but the above are sufficient to show that chloral may kill suddenly and unexpectedly.

An observation of Vulpian [46] throws much light upon these sudden deaths. He found that galvanization of a divided vagus would cause in a chloralized animal not momentary, but permanent, arrest of respiration, if the centric end was selected, or permanent diastole of the heart if the distal part of the nerve was attacked. It is very probable that in a man under the influence of chloroform or of chloral, death may be precipitated by a slight peripheral inhibitory irritation. We think the practical deduction from the known facts is that twenty grains (1.3 Gm.) is the highest safe dose of chloral ; that this amount should not be repeated oftener than once an hour, and, when sixty grains have been taken, not again for some hours, unless in very urgent cases, as acute tetanus or violent chorea threatening speedy dissolution.

CHLORALAMID.—Under the name of *chloralamid*, *chloralformamid* (a compound of chloral and formamid) has been used as an hypnotic. It is a slightly bitter crystalline substance, soluble in twenty parts of water and one and a half parts of strong alcohol. It is decomposed by hot water, but its solution in cold water is moderately permanent ; it is rapidly decomposed by alkalies. In the lower animals, chloralamid produces lethargy, narcosis, sleep, and, finally, if it has been taken in sufficient amount, death from failure of respiration. According to Langgaard,[1] in the rabbit the sleep is accompanied by pronounced decrease in the amount of air drawn in and out of the lungs, and pronounced lessening of the blood-pressure. These results, however, are scarcely in accordance with those of other observers. Otto Halasz [2] found the blood-pressure very slightly affected. Von Mering and Zuntz have shown that the fall in the air movements of respiration obtained by Langgaard was not greater than that which results from sleep, and also obtained deep sleep and even complete anæsthesia in the rabbit without fall of the arterial pressure.

In a series of experiments made by David Cerna and H. C. Wood in the laboratory of the University, it was found that the influence of chloralamid upon the circulation is very feeble, only the largest toxic dose lowering the arterial pressure at all. In the dog the respirations were

always enormously hurried by the drug, although no experiments were made to determine the absolute amount of air moved. The action of the drug upon the spinal cord was also very feeble, and no perceptible influence was shown upon the nerves and muscles ; but the effect upon the cerebral cortex was very pronounced.

THERAPEUTICS.—Our experience with chloralamid seems to be in accord with the general verdict, that it is an hypnotic, slower in action and scarcely equal in certainty to chloral ; it usually does not cause any unpleasant after-effects, but sometimes produces confusion, giddiness, and headache. It has been especially recommended by Hagemann and Hüfler[3] for the relief of cardiac *asthma*. Our knowledge of its physiological action seems to show that the assertions of various clinicians, that it is better borne than chloral in cases where there is cardiac weakness, have a foundation in fact. It should be given in doses of from thirty to fifty grains (1.9–3.2 Gm.), administered in watery solution or capsules half an hour before expected time of sleep.

CHLORALOSE occurs in small crystals, having a very bitter and disagreeable but not acrid taste. It is freely soluble in hot water, slightly so in cold water. It was first brought forward as a remedial agent by Hanriot and Richet,[1] who state that five grammes of it will produce in a dog of ten kilogrammes' weight symptoms of intoxication followed by a most profound sleep in which all sensibility is lost, although the reflex activities are greater than normal ; that upon the circulation it has but little power, the arterial pressure, even when there is profound unconsciousness, being scarcely affected ; that during the unconsciousness not only is the motor side of the spinal cord more active than normal, but the cerebral cortex is excessively excitable, the animals experimented upon offering a strong contrast with chloralized dogs, in which the cerebral cortex is almost devoid of responding power. The statements of its discoverers, that, taken in doses of five grains, it would produce in man a profound sleep lasting for many hours, and not followed by unpleasant after-effects, have not been sustained. Its action is very variable ; the dose of ten grains will in many cases produce no effect, and yet in other cases has caused complete unconsciousness with marked cyanosis and slowing of the pulse. Its therapeutic influence has frequently been attended by very unpleasant symptoms, such as tremors, partial or general paralysis, great slowing of the pulse and cardiac depression, involuntary discharge of urine during sleep, excessive vomiting, and delirious intoxication. In our experience, though occasionally useful, the drug has not proved generally satisfactory. Dose, five to ten grains (0.3–0.65 Gm.).*

CHLORAL-CAMPHOR.—Equal parts of chloral and camphor rubbed together produce a clear liquid, whose local application to the skin occa-

* See *British Medical Journal*, 1893, ii. For cases of unpleasant action, see *Schmidt's Jahrb.*, ccxlv. ; also *Revue Neurolog.*, 1894, ii.

sions tingling, but never blisters, and has been commended in *pruritus*, *neuralgia*, *toothache*, and other painful disorders. According to D. B. Simmons, in doses of ten to twenty drops, it is a powerful sedative narcotic in *mania*, etc. A drachm of it swallowed by mistake produced very severe prostration, feebleness of the pulse, vomiting, fifteen "coffee-ground" stools, and narcotism, with brief semi-delirious periods, lasting for four days.[1]

Butyl-Chloral Hydrate.—This substance, formed by the action of chlorine gas upon aldehyde, crystallizes in small glittering tables, is soluble with difficulty in water, and when in solution breaks up in the presence of an alkali into sodium chloride, sodium formate, and bichlorallylene. Under the name of *croton-chloral*, it was introduced into practical medicine by Oscar Liebreich,[1] because he found that, whilst acting in general like chloral, it depressed less powerfully the pulse and respiration, and especially affected the trigeminal nerve, lessening its sensibility before the appearance of narcosis, a drachm of it producing complete anæsthesia of the head and eyeballs. According to Liebreich, toxic doses produce deep sleep, trigeminal anæsthesia, and arrest of respiration, the circulation being maintained with great tenacity. These assertions of Liebreich have not, however, been sustained. J. von Mering found that the cornea remained sensitive until respiration was reduced to half its normal rate ; that in dogs, cats, and rabbits the drug, in small or in large dose, lessened the blood-pressure, and when brought in concentrated form in contact with the heart, arrested its movements. These results have been confirmed by E. Lahousse[2] and H. Windel Schmidt,[3] so that it is very difficult to perceive wherein the action of croton-chloral practically differs from that of chloral.

Croton-chloral was asserted by Liebreich to be very powerful in relieving *neuralgia*, *tic douloureux*, and other painful affections of the trigeminus, and considerable support has been given by clinicians to his statement. On the whole, however, the drug has failed to sustain itself, and is at present but little used : that it has any greater effect than chloral is very doubtful. It is usually administered in doses of from five to twenty grains (0.32–1.3 Gm.), in syrup. The safest plan is to give five grains every half-hour until thirty grains have been taken or relief afforded. Liebreich uses it according to the following formula : butyl-chloral hydrate, five to ten parts ; glycerin, twenty parts ; distilled water, one hundred and thirty parts. Dose, half an ounce, followed in five minutes by a second, and ten minutes later by a third unless relief is afforded.

SULPHONAL.

This substance, whose proper chemical name is *diæthylsulfondimethylmethan*, was made by E. Baumann in 1886, and first physiologically and clinically reported upon by A. Kast.[1] It occurs in thick colorless prisms, soluble in eighteen to twenty parts of boiling water, not solu-

ble in one hundred parts of cold water, slightly soluble in ether, benzol, chloroform ; tasteless, odorless, and of very persistent constitution.

PHYSIOLOGICAL ACTION.—*Local Action.*—*Elimination.*—Sulphonal is not at all irritant, and, indeed, locally it appears to be inert. Owing to its great insolubility it is absorbed very slowly from the stomach, the method of its absorption being at present unknown. When taken in large amount it escapes to some extent from the kidney unchanged, but the greater portion of it is converted into an organic sulphur compound, which, according to the researches of W. J. Smith (confirmed by Baumann and Salkowski[2]), is probably *æthyl-sulphonic acid.*

General Action.—The symptoms which are produced in man by even large therapeutic doses of sulphonal are simply quiet sleep, out of which the patient wakes after some hours in his normal condition, or not rarely with a certain amount of giddiness and lack of mental tone. Probably on account of the difficulty of its absorption, with the consequent escape of it from the alimentary canal, sulphonal has very rarely produced death when taken in a single dose.

In one case recovery occurred after one hundred and twenty grains, although there were complete abolition of the reflexes and loss of the radial pulse.[3] E. Neisser[4] has recorded a case in which one hundred grammes caused a profound sleep lasting ninety hours, a fall of bodily temperature to 96° F., and a symmetrical minutely papulous eruption upon the hands, but no great disturbance of the heart or breathing or of the reflexes ; after recovery there was a marked ataxia of speech and movement which disappeared in a week.

That the single dose of sulphonal may prove fatal is, however, established by the following cases :

Petitt[5] states that he has seen coma ending in death produced in a woman by two grammes. In a case recorded by G. Hoppe-Seyler and Ritter[6] fifty grammes produced death in seventy hours, the symptoms having been coma, cyanosis, and high fever. The expired air had the odor of mercaptan, and the urine contained unaltered sulphonal. Pronounced fatty necrosis of the intestinal and renal epithelium, fatty degeneration of the heart, and broncho-pneumonia were found in the body. The broncho-pneumonia was believed by Hoppe-Seyler to be the result of the aspiration of the contents of the mouth and gullet, due to the insensibility of the epiglottis.

In the frog, the dog, and the rabbit sulphonal produces sleep, which, if the dose be sufficiently large, deepens into coma, and is accompanied by paresis, tremors, and convulsions. Knoblauch affirms that not infrequently the loss of power in the hind legs precedes sleep, and that weakness and ataxia are prominent symptoms after large doses. The convulsions, which are said to be epileptic, are produced by very large toxic doses only.

Our knowledge of the physiological action of sulphonal is very imperfect. Its dominant influence is upon the cerebral cortex. According to Kast, the blood-pressure is not altered by doses which produce sleep, and

the rise of arterial pressure noticed by Shick in non-curarized animals may have been produced by failure of respiration. It probably depresses the motor spinal cord, although this has not been proved, and Shick states that in some of his experiments the reflex activity was increased, and that the decline of the reflexes is in fact due to stimulation of Setschenow's centre. According to Shick, it has no influence upon the motor or sensory nerves, nor upon the muscles.

Kast found that there is neither microscopic nor spectroscopic blood changes in animals acutely poisoned by the drug. The drift of the present evidence indicates that sulphonal has no distinct effect upon tissue change, but the matter is *sub judice.**

THERAPEUTIC USE.—Sulphonal is a valuable hypnotic, having, however, little or no analgesic effects, and being extremely slow in its action and scarcely as certain and satisfactory as is trional. Sleep usually develops in from a half to one hour after the dose, in most cases gradually, but sometimes with abruptness. It is usually quiet, and not followed by any disagreeable after-effects, although sometimes mental confusion and lassitude remain during the following day; these after-results being, in our experience, especially apt to occur in cases in which there is a distinct depression of the brain-nutrition. Where the sleeplessness is due to pain, sulphonal is usually not serviceable; but in the insomnia of insanity it often acts well. Later experience, however, does not seem to carry out the original assertion of Kast, that sulphonal is especially useful in cases of insomnia from cardiac diseases. In such affections it appears to be not only an uncertain, but even a dangerous drug, inferior to chloral.† At present this disagreeable action of the drug does not seem to be explainable by any influence exerted upon the heart. It is possible that it is due to irritation of already congested kidneys.

The action of sulphonal upon the reflexes would indicate its employment in spasmodic diseases, and it has been used with asserted good results in *epilepsy*, *hiccough*, *chorea*, and *nocturnal cramps;* according to E. Andrews,[7] it is very effective against the *spasm* of *fractures.* It has also been commended as a sexual sedative in *chordee* and *spermatorrhœa.* In our own practice, sulphonal given an hour after meals has seemed to have value as an intestinal antiseptic. It is asserted that it is a very useful remedy in colliquative *night-sweats.*

TOXICOLOGY.—Occasionally even the single dose of sulphonal produces nausea (even severe gastric pain: Dauthville[8]), languor, headache, depression, or pronounced mental disturbance. In rare cases sulphonal causes excitement.

* The most important papers are those of Gritzka (*Inaug. Dis.*, Berlin, 1891), W. J. Smith (*London Pract.*, 1889 and 1892), and Martin Hahn (*Virchow's Archiv*, CXXV.). John Gordon (*British Med. Journ.*, 1893, i.) has found that in weak solution sulphonal and urethan retard slightly the action of pancreatin solution upon starch, strong solutions of the drug having no effect; that chloralamid, antifebrin, and antipyrin are without such power; but that paraldehyde, whether in weak or strong solution, has a very profound effect.

† See Joachiam (*Therap. Monatsh.*, iii.); also Schmey (*Ibid.*, 1888, ii.).

Chronic sulphonal-poisoning usually ends in death, since out of twenty recorded cases which we have collected seventeen terminated fatally. The prodromic symptoms are probably always present, but certainly in a large majority of cases have been overlooked, and have nothing in them that is at all characteristic. They are increasing lassitude and weakness, nausea, and gastro-intestinal disturbance as shown by diarrhœa or constipation. Usually the first symptom noted is the red coloration of the urine, which deepens until the fluid becomes of a dark red color, staining the linen upon which it falls. Usually this coloration of the urine is soon followed by obstinate constipation, violent vomiting, spasm of the abdominal muscles, and tenderness upon pressure in the region of the liver and stomach. At the same time there develop irregularity of gait, ataxia, suppression of perspiration, paresis of the upper extremities or perchance paresis of irregular groups of muscles, pronounced weakness of the legs, loss of the patellar and other reflexes, paræsthesia, muscular spasms, and finally a condition of profound collapse, with albuminous, hemorrhagic, or suppressed urine, ending in death. After death, wide-spread fatty degeneration, involving in some cases the heart, but especially affecting the liver and kidney, has been found. In some cases the renal trouble has been confined almost to a glomerular or cortical nephritis.

An important fact is that a chronic poisoning ordinarily develops with apparent rapidity, and, notwithstanding the suspension of the remedy, usually goes on steadily, though it may be slowly, to a fatal issue. It has been shown by Salkowski (confirmed by Kast[9]), that æthyl-sulphonic acid is not poisonous, and hæmatoporphyrin appears also to be free from toxic properties; so that the symptoms of chronic poisoning are probably due to an accumulation of sulphonal in the system, and are of largely primary and not of secondary character, though some of them may be in fact uræmic. The explanation of the occurrence of hæmatoporphyrinuria is at present very difficult; frequently it does not come on until several days after the ingestion of the last dose. In a fatal case of acute poisoning reported by Hoppe-Seyler and Ritter it was not present. As has been demonstrated by Garrod and Hopkins,[10] the urine of patients taking sulphonal does not ordinarily contain more hæmatoporphyrin than is often seen in health. It is generally thought that the hæmatoporphyrin is a decomposition product of hæmatin, and Stokvis[11] believes that the hæmatoporphyrinuria is due to the absorption of altered blood from hemorrhages which have been produced in the mucous membrane of the stomach and intestines by sulphonal, an explanation which is rejected by Kast and Weiss,[12] and also by Garrod and Hopkins, for apparently sufficient reasons. The observation of Garrod and Hopkins, that the increase of urinary hæmatoporphyrin is not accompanied by a corresponding increase in the excretion of iron, and the fact that in the cases recorded by Percy Smith there was no lessening in the blood of the red blood-corpuscles or of the hæmoglobin, lend probability to the assertion

of Quincke (confirmed by Herting[13]), that the coloring-matter of the urine is not in reality hæmatoporphyrin, differing from it in its spectroscopic lines. Franz Müller, however, found in a case of sulphonal-poisoning which recovered that the hæmoglobin fell during the period of red urine to forty-five per cent., returning afterwards to eighty-five per cent; whilst Hoppe-Seyler believes that the anatomical changes in sulphonal-poisoning are really secondary to the destruction of the red blood-disks. After death from sulphonal-poisoning Stern and Oswald have detected necrotic changes in the epithelium of the renal glomeruli and of the secreting portions of the tubules, whilst Kast found in dogs hemorrhage into the glomerular capsules. The early recognition of hæmatoporphyrin in the urine is best made by means of the spectroscope.

The exanthem of sulphonal-poisoning may be bullatous, but is usually a minutely papulous eruption, which has been described by some as resembling that of measles, by others as like that of scarlet fever. It is not rarely symmetrical, and often shows a disposition to follow the nerve-trunks, so that it is probably neurotic.

In the treatment of sulphonal-poisoning the first attention should be given to seeing that the bowels are well opened, which usually requires very energetic measures. The use of the sodium carbonates, as suggested by Müller,[14] probably offers the best hope of any therapeutic measures.* Large amounts of water, which may carry the alkali, should be introduced both by the mouth and by hypodermoclysis, to wash the poison out of the system.

ADMINISTRATION.—The dose of sulphonal is from ten to forty-five grains (0.7–3 Gm.). It is absorbed with difficulty, and should always be administered in fine powder diffused in water or milk, or enclosed in capsules. We have seen compressed pills of sulphonal pass through the body unchanged, and have no doubt that the reported great slowness or even failure of action has often depended on improper methods of administration. It should be an invariable rule when sulphonal is given continuously every two weeks to suspend its employment for some days, so as to allow the system to clear itself ; and the urine should also always be carefully watched and the first appearance of the red tint be the signal for immediate withdrawal.

TRIONAL.

Trional is a disulphon, which occurs in commerce as a colorless, shining, bitter, crystalline powder, soluble in three hundred and twenty parts of cold, easily soluble in hot, water ; also in alcohol and ether. *Tetronal*, a closely allied hypnotic, is never employed at present.

Locally trional seems to be inert. It is absorbed much more rapidly than is sulphonal and acts much more promptly. Concerning its elimination we have no information. Given to man in doses of fifteen to

* Alkaline waters, however, in Pollitz's case (*Vierteljahr. f. Gerichtl. Med.*, 1898, v.) apparently failed to do any good.

twenty grains, it usually causes in from fifteen minutes to an hour a quiet, apparently normal, sleep. We know of no cases of dangerous acute poisoning by it in man ; one hundred and twenty grains of it, taken at a single dose, produced no serious symptoms. Although, probably owing to its greater solubility, it is less apt than is sulphonal to cause chronic poisoning, a number of cases have occurred. The symptoms have been great lassitude, giddiness, headache, tinnitus aurium, gastro-intestinal pain, vomiting, obstinate constipation, pronounced tremors, ataxia, especially shown by an uncertain gait, and in one or two cases even a pronounced general paresis, with loss of control over the sphincter ; also lessened secretion of the urine, and hæmatoporphyrinuria. Strangury has been noted, whilst even the therapeutic dose may cause excessive acidity of the urine. These symptoms differ from those produced by sulphonal chiefly in that the hæmatoporphyrinuria is less pronounced, and in that the premonitory symptoms are more marked. The treatment is the same as that of sulphonal-poisoning.*

Beyond the fact that the dominant influence of trional is upon the cerebrum, we have no definite knowledge as to the way in which it acts. According to Haenel,[1] the rate of the mental function is distinctly lessened by it, and continues slow for some time after the sleep period. If it be true, as asserted by Egasse,[2] that in animals trional sleep is attended by increase in the activity of the reflexes, it probably stimulates the spinal cord. Kronfeld,[3] as the result of sphygmomanometrical studies, affirms that the blood-pressure is always lowered during sleep caused by trional, the fall being due, in his belief, to depression of the vaso-motor centres.

When prompt action is desired, trional is best given in hot water or hot milk, though the powder in capsules is effective.

MINOR SOMNIFACIENTS.

In the tenth edition of this treatise there are considered in detail several substances which had been brought forward as practical hypnotics. As they have, however, with perhaps the exception of urethan, entirely failed of practical success, we note them here very briefly.

PARALDEHYDUM—PARALDEHYDE. U. S.—*Paraldehyde* is a colorless liquid, having a boiling point of 123.5° C., and an extremely disagreeable odor and taste, which was first brought to the notice of the profession by Cervello. It is a distinct local irritant, is slowly absorbed, and is eliminated with the urine, to which it imparts its odor. In moderate doses it produces sleep, with diminished sensibility and muscular tone. In toxic doses it causes coma, great muscular relaxation, progressively diminishing respiration, and at last death from asphyxia without convulsions. According to Gordon, it is an active depressant to the cerebral cortex, to

* For cases of poisoning, see Vogel (*Berl. Klin. Woch.*, 1899, 875) ; also *Münch. Med. Woch.*, xiii. 928.

the respiratory centres, to the spinal cord, to the motor and sensory nerve-trunks, and also to the muscle. Its influence upon the circulation is comparatively feeble, though large enough doses lower the arterial pressure and lessen the heart's action. Concerning its influence upon the blood itself, there is much confusion of statement by investigators; it probably is one of those agents that produce methæmoglobin.

Paraldehyde has little influence over pain, but has been used to a considerable extent as an hypnotic, and also as a motor relaxant in spasm. Its uncertainty of action, and more especially its exceedingly nauseous taste, the disagreeable odor which it is apt to impart to the breath, and its great tendency to disturb digestion, are the chief causes of its desuetude. Its prolonged use has in various cases been followed by marked disturbances of nutrition, as shown by nasal ulcers, skin eruptions, and vaso-motor disturbances. Krafft-Ebing has reported cases of the paraldehyde habit, with delirium and other untoward results. The dose is one fluidrachm (3.75 C.c.), which must be taken well diluted.

URETHAN is a crystalline carbonate of ethylic ether, soluble in one part of water; originally suggested by Schmiedeberg as a possible hypnotic. Its dominant physiological action seems to be upon the cerebral cortex and upon the motor side of the spinal cord. According to Schmiedeberg[1] it has very little influence upon the circulation, the arterial pressure remaining normal even during deep narcosis. In clinical experience it has, however, been found to be very uncertain in its action, though it has occasionally been used with satisfactory results not only as an hypnotic but also as an anticonvulsant in puerperal and other serious *eclampsia*. According to Kraepelin, the full dose is forty-five grains (3 Gm.), but seventy-five grains have been given without much effect.

AMYLENE HYDRATE, a clear, colorless liquid, of a penetrating odor, soluble in eight parts of water, was brought forward in 1885 by Von Mering and Thierfelder,[1] and is said by its discoverers to act very much like chloral, only requiring double the dose. Five grammes of amylene hydrate inhaled by man produced profound narcosis, paralysis of the extremities, dilated pupil, abolished reflexes; slow, deep, irregular respiration; failing pulse, with depression of the temperature. The drug appears to differ from most other hypnotics in being a poison both to the voluntary and cardiac muscles. The assigned dose is thirty to forty minims (2–2.5 C.c.).

METHYLAL, brought forward by Personali, is said by Motrokhin, when inhaled by man in doses of two ounces, to produce sleep with loss of sensibility, without any effect upon the heart. Popoff, however, affirms that it acts directly upon the cardiac muscle. It is so rapidly absorbed and eliminated that it should probably be considered an anæsthetic rather than an hypnotic, and it is said that it very rapidly loses its power over

patients. The commencing dose of Mairet and Combemale is seventy-five grains; the maximum dose is one hundred and twenty grains (4.8–7.8 Gm.).

HYPNONE or ACETOPHENONE, originally suggested by Dujardin-Beaumetz, according to various authorities acts more powerfully as a paralyzant than as an hypnotic, and has been condemned by a large number of clinicians. The maximum dose given by Rey, without, however, the production of sleep, was sixty drops, or twenty-three grains (1.5 Gm.).

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AMYLENE HYDRATE.

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FAMILY IV.—DELIRIFACIENTS.

In the present group are considered medicines whose preparations, when taken into the system, cause marked dilatation of the pupil, and act upon the cerebral nerve-cells so as to produce delirium.

EXTRACTUM CANNABIS INDICÆ—EXTRACT OF INDIAN CANNABIS. U. S.

The alcoholic extract of Indian hemp is a blackish, resinous extract, of a decided narcotic odor and a peculiar taste. In the East hemp and its educts are used as narcotic stimulants. *Gunjah* is the dried plant as sold in the bazaars of Calcutta for smoking. *Churrus* is the resinous exudation with the epidermis, etc., scraped off the leaves. *Hashish* is an Arabian preparation of the drug. The resin, which represents the activity of hemp, is sometimes known as *Cannabene*. It is best obtained by precipitating the saturated tincture with water containing an alkali. Hemp also contains a trace of volatile oil. The nature of the active principle is still entirely uncertain.

Physiological Action.—When given in full doses, cannabis indica produces a feeling of exhilaration, with a condition of revery, and a train of mental and nervous phenomena which varies very much according to the temperament or idiosyncrasies of the subject, and very probably also, to some extent, according to the nature of his surroundings. The sensations are generally spoken of as very pleasurable; often beautiful visions float before the eyes, and a sense of ecstasy fills the whole being; sometimes the venereal appetites are greatly excited; sometimes loud laughter, constant giggling, and other indications of mirth are present. Some years since, in experimenting with an extract made from the American plant, H. C. Wood took a large dose, and described the result as follows:[1]

"About half-past four P.M., September 23, I took most of the extract. No immediate symptoms were produced. About seven P.M. a professional call was requested, and, forgetting all about the hemp, I went out and saw my patient. While writing the prescription, I became perfectly oblivious to surrounding objects, but went on writing, without any check to or deviation from the ordinary series of mental acts connected with the process, at least that I am aware of. When the recipe was finished, I suddenly recollected where I was, and, looking up, saw my patient sitting quietly before me. The conviction was irresistible that I had sat thus many minutes, perhaps hours, and directly the idea fastened itself that the hemp had commenced to act, and had thrown me into a trance-like state

of considerable duration, during which I had been stupidly sitting before my wondering patient. I hastily arose and apologized for remaining so long, but was assured I had only been a very few minutes. About seven and a half P.M. I returned home. I was by this time quite excited, and the feeling of hilarity now rapidly increased. It was not a sensuous feeling, in the ordinary meaning of the term; it was not merely an intellectual excitation; it was a sort of *bien-être*,—the very opposite to *malaise*. It did not come from without; it was not connected with any passion or sense. It was simply a feeling of inner joyousness; the heart seemed buoyant beyond all trouble; the whole system felt as though all sense of fatigue were forever banished; the mind gladly ran riot, free constantly to leap from one idea to another, apparently unbound from its ordinary laws. I was disposed to laugh; to make comic gestures; one very frequently recurrent fancy was to imitate with the arms the motions of a fiddler, and with the lips the tune he was supposed to be playing. There was nothing like wild delirium, nor any hallucinations that I remember. At no time had I any visions, or at least any that I can now call to mind; but a person who was with me at that time states that once I raised my head and exclaimed, 'Oh, the mountains! the mountains!' While I was performing the various antics already alluded to, I knew very well I was acting exceedingly foolishly, but could not control myself. I think it was about eight o'clock when I began to have a feeling of numbness in my limbs, also a sense of general uneasiness and unrest, and a fear lest I had taken an overdose. I now constantly walked about the house; my skin to myself was warm, in fact my whole surface felt flushed; my mouth and throat were very dry; my legs put on a strange, foreign feeling, as though they were not a part of my body. I counted my pulse and found it one hundred and twenty, quite full and strong. A foreboding, an undefined, horrible fear, as of impending death, now commenced to creep over me; in haste I sent for medical aid. The curious sensations in my limbs increased. My legs felt as though they were waxen pillars beneath me. I remember feeling them with my hand and finding them, as I thought at least, very firm, the muscles all in a state of tonic contraction. About eight o'clock I began to have marked 'spells,'—periods when all connection seemed to be severed between the external world and myself. I might be said to have been unconscious during these times, in so far that I was oblivious to all external objects, but on coming out of one it was not a blank, dreamless void upon which I looked back, a mere empty space, but rather a period of active but aimless life. I do not think there was any connected thought in them; they appeared to be simply wild reveries, without any binding cord,—each a mere chaos of disjointed ideas. The mind seemed freed from all its ordinary laws of association, so that it passed from idea to idea, as it were, perfectly at random. The duration of these spells to me was very great, although they really lasted but from a few seconds to a minute or two. Indeed, I now entirely lost my power of measuring time. Seconds were hours; minutes were days; hours were infinite. Still, I was perfectly conscious during the intermissions between the paroxysms. I would look at my watch, and then after an hour or two, as I thought, would look again and find that scarcely five minutes had elapsed. I would gaze at its face in deep disgust, the minute-hand seemingly motionless, as though graven in the face itself; the laggard second-hand moving slowly, so slowly. It appeared a hopeless task to watch during its whole infinite round of a minute, and always would I give up in despair before the sixty seconds had elapsed. Occasionally, when my mind was most lucid, there was in it a sort of duplex action in regard to the duration of time. I would think to myself, It has been so long since a certain event,—an hour, for example, since the doctor came; and then reason would say, No, it has been only a few minutes; your thoughts or feelings are caused by the hemp. Nevertheless, I was not able to shake off this sense of the almost indefinite prolongation of time, even for a minute. The paroxysms already alluded to were not accompanied by muscular relaxation. About a quarter before nine o'clock, I was standing at the door, anxiously watching

for the doctor, and when the spells would come on I would remain standing, leaning slightly, perhaps, against the door-way. After a while I saw a man approaching, whom I took to be the doctor. The sounds of his steps told me he was walking very rapidly, and he was under a gas-lamp, not more than one-fourth of a square distant, yet he appeared a vast distance away, and a corresponding time approaching. This was the only occasion on which I noticed an exaggeration of distance; in the room it was not perceptible. My extremities now began to grow cold, and I went into the house. I do not remember further, until I was aroused by the doctor shaking or calling me. Then intellection seemed pretty good. I narrated what I had done and suffered, and told the doctor my opinion was that an emetic was indicated, both to remove any of the extract still remaining in my stomach, and also to arouse the nervous system. I further suggested our going into the office, as more suitable than the parlor, where we then were. There was at this time a very marked sense of numbness in my limbs, and what the doctor said was a hard pinch produced no pain. When I attempted to walk up-stairs, my legs seemed as though their lower halves were made of lead. After this there were no new symptoms, only an intensifying of those already mentioned. The periods of unconsciousness became at once longer and more frequent, and during their absence intellection was more imperfect, although when thoroughly roused I thought I reasoned and judged clearly. The oppressive feeling of impending death became more intense. It was horrible. Each paroxysm would seem to have been the longest I had suffered; as I came out of it, a voice seemed constantly saying, 'You are getting worse; your paroxysms are growing longer and deeper; they will overmaster you; you will die.' A sense of personal antagonism between my will-power and myself, as affected by the drug, grew very strong. I felt as though my only chance was to struggle against these paroxysms,—that I must constantly arouse myself by an effort of will; and that effort was made with infinite toil and pain. I felt as if some evil spirit had control of the whole of me except the will-power, and was in determined conflict with that, the last citadel of my being. I have never experienced anything like the fearful sense of almost hopeless anguish and utter weariness which was upon me. Once or twice during a paroxysm I had what might be called nightmare sensations: I felt myself mounting upward, expanding, dilating, dissolving into the wide confines of space, overwhelmed by a horrible, rending, unutterable despair. Then, with tremendous effort, I seemed to shake this off, and to start up with the shuddering thought, Next time you will not be able to throw this off, and what then? Under the influence of an emetic I vomited freely, without nausea, and without much relief. About midnight, at the suggestion of the doctors, I went up-stairs to bed. My legs and feet seemed so heavy I could scarcely move them, and it was as much as I could do to walk with help. I have no recollection whatever of being undressed, but am told I went immediately to sleep. When I awoke, early in the morning, my mind was at first clear, but in a few minutes the paroxysms, similar to those of the evening, came on again, and recurred at more or less brief intervals until late in the afternoon. All of the day there was marked anæsthesia of the skin. At no time were there any aphrodisiac feelings produced. There was a pronounced increase of the urinary secretion. There were no after-effects, such as nausea, headache, or constipation of the bowels."

The sense of prolongation of time present in most cases of hemp intoxication is evidently due to the immense rapidity of the succession of ideas. The mind measures time by the duration of its own processes, and when an infinitude of ideas arise before it in the time usually occupied by a few, time becomes infinitely prolonged to the mind. It is a lifetime in the minute. A very common mental phenomenon, not easily explained unless as a result of disassociation of the cerebral hemispheres,

is a condition of double consciousness, a sense of having two existences, of being at the same time one's self and somebody else.

In some cases Indian hemp produces, in addition to or even in the place of the symptom already spoken of, marked disturbances of motility. Convulsions have been noticed by Lawrie,[2] and local spasms, with salaam convulsions, by F. H. Brown. According to O'Shaughnessy, the induction of catalepsy is not rare among the Hindoos.

Whatever may be the symptoms of the first stage, sooner or later, if the dose be sufficient, drowsiness comes on. Generally, before it is marked, partial anæsthesia, often with partial loss of strength, is manifested, especially in the lower limbs. The pupils are dilated, the pulse is quickened, and finally the subject falls into a heavy sleep, out of which he generally awakes hungry, without any of the wretched gastric sensations or the malaise felt after an opiate. Confusion of thought, however, may persist for some hours. Cannabis exerts no constipating influence upon the bowels, and appears to increase, rather than decrease, the excretion of the kidneys.

In the dog, hemp extract causes exaltation followed by profound sleep (Hans Zeitler,[3] H. A. Hare[4]). That the drug has very little influence upon the vital functions is shown by the enormous amounts required to kill. Hare noted both in the dog and in the frog heightened, followed by markedly lessened, reflex activity. The loss of reflex activity was the result of an influence exerted upon the sensory side of the cord or upon the sensory nerve-trunk, the anæsthesia in the frog being complete at a time when voluntary movement was preserved; further, when the drug was applied directly to the nerve-trunk it produced sensory palsy. Although probably a local anæsthetic, cannabis indica is too irritant to be applied to delicate mucous membranes.

THERAPEUTICS.—Hemp has been used in this country chiefly for the *relief of pain*, but also to some extent as an *hypnotic*. As an *analgesic*, it is very much inferior to opium, but may be tried when the latter is for any reason contra-indicated. In full doses, in *neuralgic* pains, it certainly often gives relief. It has been very largely employed to induce euthanasia in the advanced stages of *phthisis*, and constitutes, it is said, a popular nostrum employed for that purpose. In *tetanus*, Indian hemp has been used quite largely, and is sometimes apparently an aid to other remedies; it should be given to intoxication. As first suggested by Seguin, hemp extract, administered for months continuously in such doses as will keep just within the limit of distinct physiological effects, is often effective in *migraine*.

ADMINISTRATION.—Extract of hemp is a very unsatisfactory drug from the fact that one-eighth of a grain of one extract will produce decided intoxication, and many grains can be taken of another extract that cannot be distinguished physically or chemically from the first specimen. The only way of using it with advantage is for the practitioner to try various samples in ascending doses, and use those which are active in the

dose which he has found to be effective. The foreign extracts are, on the whole, more reliable than those made in America. It should always be borne in mind that, though the symptoms may seem alarming, there is much less danger in intoxication from hemp than from alcohol. No cases of fatal poisoning have been recorded. The dose of the official tincture (TINCTURA CANNABIS INDICÆ—fifteen per cent., U. S.) is thirty minims (2 C.c.); of the fluid extract (EXTRACTUM CANNABIS INDICÆ FLUIDUM, U. S.), one minim (0.12 C.c.); of the extract (EXTRACTUM CANNABIS INDICÆ, U. S.), one-sixth to one-fourth of a grain (0.01–0.016 Gm.): all of these doses may be indefinitely increased until symptoms are produced. Notwithstanding the assertions of Fronmüller and Hiller, the *tannate of cannabene* of Merck has in our trials of it seemed to be inert.

BELLADONNÆ FOLIA—BELLADONNA LEAF. U.S.
BELLADONNÆ RADIX—BELLADONNA ROOT. U.S.

The leaves and root of Atropa Belladonna, an herbaceous perennial, a native of Europe, but cultivated in this country, and attaining a height of some three feet. The dried leaves are oval, entire, on a short footstalk; they have a faint narcotic odor, and a sweetish, sub-acrid, slightly nauseous taste. The dried cylindrical branched root is from one to several inches in diameter, much longer, fibrous, externally reddish brown, internally whitish, almost odorless, with a very feeble sweetish taste.

ATROPINA. U.S.

Atropine* occurs in silky prismatic and acicular, often aggregated, crystals, of a bitter, burning taste, without odor, soluble in three hundred parts of cold and fifty-eight of boiling water, forty of benzole, thirty of ether, three of chloroform, and eight of alcohol. It is most abundant in the root, and, according to M. Lefort,[1] in that of young plants.

PHYSIOLOGICAL ACTION.—*Local Action.*—*Elimination.*—Atropine is not irritant, but when locally applied in sufficient concentration is probably paralyzant to most higher forms of protoplasm, overpowering the capillary walls, the sensory and motor nerves, and even muscular and glandular cell-action. A. Zeller[2] has found that a one per cent. solution of atropine brought in contact with the blood, outside of the body, checks the movements of the corpuscles. Atropine is absorbed with great rapidity, and probably enters into all the excretions of the body, as it has been found in all the tissues of the poisoned individual, and S. Fubini and O. Bonanni[3] have detected it in the milk. It, however, chiefly escapes with the urine; hence in poisoning the nature of the case can usually be established by dropping the urine of the patient in the eye of a cat or other domestic animal, when mydriasis will be produced.†

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* For the relations of atropine to other mydriatic alkaloids, see HYOSCINE, page 138.

† For a chemico-physiological study of *tropine* and other derivatives from atropine, see *Archiv f. Exper. Pathol. u. Pharm.*, v. 403.

General Action.—Usually the only symptom induced in man by the smallest physiological dose of atropine (one-hundredth to one-sixtieth of a grain) is dryness of the throat and mouth, and possibly some disorder of vision. When larger amounts are given, this dryness is more intense, and is associated with redness of the fauces, dilated pupils, disordered vision, and possibly diplopia. The pulse is sometimes at first rendered less frequent, but this decrease is very transient, and certainly in many cases cannot be demonstrated at all. After a toxic dose of the alkaloid, often from the first, certainly always in a short time, the heart's beats become excessively rapid, the pulse rising to 120, or even 160; and in a little while a peculiar bright red flush appears on the face and neck, and may spread over the whole body. This erythema resembles the rash of scarlet fever, but lacks punctation, and is usually not followed by desquamation. Early in atropine-poisoning there may be forcible expulsion of urine, and even erections of the penis; later there is urinary retention. With the symptoms above enumerated, intellection may remain perfect; but there is generally some lightness of head, giddiness, and confusion of thought, as well as a staggering gait and restlessness. Occasionally, even medicinal doses cause spectral illusions. Drowsiness is not a usual or at all characteristic symptom. When the dose has been sufficient there develops a peculiar talkative, wakeful delirium, in which the patient lives in a world of his own, engrossed by spectres and visions which throng him, and completely oblivious to the surrounding realities. Thus, we have seen a lady remain for a long time stooping and holding fast to the bed-post, to which she talked in the most voluble manner, as though it were an intelligent, living entity. Sometimes this delirium is wild, and the patient almost uncontrollably violent. After a time, sleep may come on, and on waking complete consciousness may be regained, or the symptoms may gradually subside. Lividity of the face and evident imperfect aëration of the blood are not seen in atropine-poisoning, except in the stage of imminent peril. When an enormous dose of the alkaloid has been taken a fatal stupor with muscular relaxation may develop almost at once; or severe convulsions may appear and persist, with or without furious maniacal delirium. Probably, however, in all fatal cases stupor and muscular paralysis finally develop; and although there is marked failure of the circulation, the immediate cause of death is asphyxia, produced by depression both of the respiratory nerve-centres and of the respiratory nerve-trunks. Congestion of the lungs and of the membranes, and even of the substance of the brain and cord, may be found after death, and, according to M. Lemattre,* congestion of the retina is an almost characteristic lesion.

Upon the lower animals belladonna to a great extent acts as upon man, although its influence is much less powerful in them, and very much

* Quoted by Tardieu (*Sur l'Empoisonnement*, Paris, 1867, 752).

larger doses are required. Seeming differences of action are in most cases simply apparent, not real.

In the dog, as in man, the pulse-rate is very greatly increased by atropine, while in the rabbit it is not. As will be shown hereafter, the rise of the pulse-rate caused by atropine is largely due to paralysis of the par vagum. Atropine paralyzes the par vagum in the rabbit as much as in the dog, but in the domestic rabbit pneumogastric paralysis, by section or otherwise, is never followed by a rise of the pulse-rate at all comparable to that seen under similar circumstances in the dog. Evidently the action of the drug is identical in the two cases, although the symptoms are different. In their sensitiveness to atropine animals differ very much, and, as a general rule, herbivora are less susceptible than carnivora. Thus, the rabbit may be fed for days entirely upon belladonna-leaves without injury, and many grains of atropine are necessary to kill him. Pigeons we have found will often recover after the hypodermic injection of two grains of atropine, and, according to Féré, 1.75 grammes taken by the mouth will not kill a hen of 2.9 kilogrammes' weight. A very curious fact, which we have repeatedly verified, is that the pupils in pigeons cannot be dilated by the use of belladonna. According to Richet, the monkey offers an extraordinary resistance to the action of atropine.

Circulatory System.—Atropine may cause a primary slowing of the pulse (very brief and only to be occasionally demonstrated), followed by an extraordinarily rapid pulse, with a very great rise in the arterial pressure; followed after a time, if the dose have been sufficient, by a progressive lowering of pressure until death is reached, the rapidity of the pulse being maintained until the end.

As in atropinized animals neither section nor galvanization of the vagi affects the pulse-rate, the increase of the pulse-rate must be largely due to paralysis of the trunk or of the peripheral endings of the vagi. The primary fall of the pulse, in accordance with the experiments of Bezold and Bloebaum,[4] is due to stimulation of the inhibitory cardiac centre; these observers having found that when atropine is injected into the carotid so as to reach the pneumogastric centres before the pneumogastric nerve-endings, there is instantaneously a great fall in the rate of the heart's beat. Of course, in the fully atropinized animal any effect of the drug upon the inhibitory centres is masked by the inability of the paralyzed vagi to carry impulses from the centre, and, in fact, only in especial cases is the primary slowing manifested.*

By large doses of atropine both the batrachian and mammalian heart are depressed and arrested in diastole, out of which they cannot be aroused by stimulation; and Bezold and Bloebaum have found that after section of the spinal cord and vagi full doses of atropine lessen at once the arterial pressure. It is therefore established that overwhelming doses of atropine act as a direct paralyzant upon the heart-muscle.

The question as to the effect of small doses has been much debated, but probably very minute quantities exert a feeble, stimulating influence

* See *Stillé's Therapeutics*, i. 725. Mitchell, Keen, and Morehouse found it in about one-third of the cases after large hypodermic injections, Da Costa in a large proportion, (*Amer. Journ. Med. Sci.*, July, 1865), and Miss Mary Putnam in some cases (*New York Medical Record*, 1873).

upon the heart;* thus, Ramson discovered that atropine causes in the heart of the octopus pronounced excitation of the muscular fibre; O. Langendorff[6] found that when the cut-off apex of the frog's heart was touched with a minute quantity of atropine it immediately commenced to beat;† and G. Beyer[7] noticed that the ventricles of the isolated terrapin's heart are enormously stimulated by minute quantities of the alkaloid, although they are arrested in diastole by larger amounts. This action of the drug upon the heart-muscle is probably the cause of the increased pulse-rate which has been noted as occurring when atropine is given after division of the vagi, although it is possible that this increase is due to stimulation of the accelerators.‡

The recorded evidence obtained by the direct observation§ of the capillaries under the microscope during poisoning of frogs by atropine is, on the whole, in favor of the view that minute doses of atropine cause contractions of the vessels; but much more decisive proof is to be obtained as to the effect of atropine upon the vaso-motor system by a study of the arterial pressure. It was first proved that the alkaloid is powerless to produce rise of the arterial pressure after separation of the vaso-motor centres, by high-up section of the spinal cord, from the blood-vessels of the body, by Bezold and Bloebaum, whose statements were confirmed in 1873 by H. C. Wood.[8] Further, Bezold and Bloebaum have found that when a small dose of atropine is injected into the carotid artery, —that is, into the vaso-motor centres,—there is an instantaneous rise of pressure. There can be no doubt that the chief factor in the great rise of arterial pressure produced by atropine is a stimulating influence upon the vaso-motor centres.

The final fall of blood-pressure in atropine-poisoning is due to its depressing influence upon the heart-muscle and upon the muscles in the walls of the capillaries. The local application of the alkaloid to the web of the frog's heart is soon followed by a complete paralytic dilatation of the vessels; further, Bezold and Bloebaum have found that the arterial muscular coats in atropine-poisoning finally lose their irritability, but that,

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* Harnack (*Archiv f. Exper. Pathol. Pharm.*, ii. 328) finds that the minutest dose of atropine increases the rapidity of the heart's action after stimulation of its inhibitory centres by muscarine and consequent slowing of its beat.

† The reports as to the action upon the rate of the frog's heart are somewhat at variance, Bowditch and Luciani having noted an increase, Gnauck[6] a lessening, in the cardiac pulsations (*Verhandl. Physiolog. Gesellsch. zu Berlin*, 1881). H. Schapiro states that this variance is accounted for by the fact which he has discovered, that whereas at high temperature (15° C.) the pulsations are diminished, at low temperature (7° C.) they are increased.

‡ See *University Med. Magazine*, May, 1891.

§ A fuller discussion of this subject may be found in the tenth edition of this book. It is omitted here because we do not think that evidence of this character is of much importance. The contraction of the capillaries by a local application may be the result of mechanical or other irritation. Moreover, the alterations in the calibre of the vessels are so slight, and are so apt to occur from other causes than the drug given, as to leave great play for the imagination of the observer,—a source of fallacy whose importance is indicated by the ever-varying results obtained by the different investigators.

so long as they retain it, galvanic stimulation of a sympathetic nerve does not fail to induce contraction in the tributary vessels.

Cerebrum.—The delirium which is so characteristic of atropine-poisoning shows that it has especial relations with the cerebral cortex. Albertoni[9] finds that neither the single large dose nor the repeated continuous dose has any power in preventing the epileptic seizure resulting in dogs from the stimulation of the motor zone of the cortex: enormous toxic doses seem only to render the response slower and less vivid. The influence of atropine upon the psycho-motor centres would, therefore, appear to be slight. It should be noted that atropine is not in a proper sense hypnotic, the stupor which it produces being due to an overwhelming of the cerebral cortical centres, and not being preceded by sleep.

Motor Nerves.—The original discoveries of S. Botkin,[10] that tying the vessels of a frog's leg, so as to shut off access of atropine to the nerve, interferes with the development of paralysis during the poisoning in such leg, and that the nerves after death from atropine-poisoning have in the frog largely lost their power of responding to galvanic currents, have been abundantly confirmed by Lemattre, by Bezold and Bloebaum (*loc. cit.*, 20), by Meuriot,[11] by Fraser, and others. Although in mammals a notable amount of functional power is retained by the motor nerve up to death from atropine, yet it is demonstrated that atropine is a distinct depressant to the motor nerves, both in the higher and in the lower animals; and, according to Bezold and Bloebaum, both the nerve-trunks and the peripheral intra-muscular nerve-endings are affected. All experimenters agree that no stage of super-excitability preceding that of depression can be discovered.

Sensory Nerves.—The action of atropine upon the sensory nerves is similar to its influence upon the motor nerves, although less powerful.* S. Botkin found that if in the atropinized frog the nerve of one leg had been protected from the poison by tying the artery, irritation of the foot of the non-protected leg at a time when that leg was completely paralyzed would cause spasm in the opposite limb whose motor nerve was protected; yet later in the poisoning, although irritation of the foot of the protected leg would cause movement in that leg, no irritation of the opposite poisoned foot was able to induce response, showing that at first the sensory nerve was intact in the paralyzed leg, but that it finally succumbed to the poison.

Meuriot found that if a frog be bound tightly around the body so as to interrupt the circulation, and then be poisoned by atropine in the front part of its body, at first irritations in any part will give rise to general spasms, but after a time in order to get any movements of the hind legs it is necessary to apply an irritant to them. Again, the hinder parts of a

* For objections to Miss Mary Putnam's paper (*N. Y. Med. Rec.*, 1873), which would indicate that the sensitive nerves are especially affected by atropine, see tenth edition of this treatise.

frog were so bound by ligatures as to cut off on the one side all communication except by the nerves, and on the other to leave free the nerve and the vessels. A large injection of atropine was then given, and when the moment came that irritation of the periphery of the leg whose circulation was free would no longer cause reflex spasms, the artery of this leg also was tied, so that both legs, the one atropinized, the other not, were now connected with the body of the frog only by their nerves. Strychnine was given hypodermically, and it was found that, while irritation of the atropinized leg had no effect, stimulation of the non-atropinized leg gave rise to general convulsions. It is plain, however, that the influence of atropine upon the sensory nerve is feeble ; for, although Botkin confirmed the experiments of Bezold and Bloebaum, he found that immersion of a sciatic nerve for some little time in a two and a half per cent. solution of the alkaloid did not, in the strychnized frog, prevent the nerve transmitting the impulse, since irritation of the foot would produce general convulsions.

Spinal Cord.—Thomas R. Fraser[12] discovered in 1869 that if a frog receive an injection of about one-thousandth part of its weight of atropine, a condition of perfect paralysis and abolition of reflex action comes on after a time, and lasts from two to four days, to be succeeded by a tetanoid stage, with violent convulsions of spinal origin and excessive excitability of the reflex centres. For reasons given in full in the tenth edition of this treatise, Fraser came to the conclusion that atropine stimulates the spinal cord, and that during the paralytic stage of the poisoning this condition of the cord is masked by the paralyzed state of the efferent nerves. This conclusion, however, has been disproved by Ringer and Murrell, who found that tying an artery so as to protect the nerve-trunks from the poison did not hasten the development of the tetanus ; and also showed that in some poisoned frogs voluntary and reflex action return before the supervention of the tetanus. It is evident that both paralysis and tetanus are due to an action upon the spinal centres, the drug so acting upon the spinal cord as first to paralyze and then intensify its reflex activity. The theory approved by Ringer and Murrell, that both the paralysis and the tetanus are due to a depressant action upon this cord, is plausible and probably correct.

According to this theory the spinal cord has within it two functions, motion and inhibition, certain cells giving off motor impulses, certain nerve-fibres inhibiting these motor impulses. In the normal cord the motor cells are under continual inhibition ; under the influence of atropine it is believed that both motor and inhibitory functions are paralyzed ; hence the general paralysis. After a time, however, the motor cells recover themselves so as to be able to generate impulses freely, although the inhibitory function of the cord is still depressed, the effect being an apparently true spinal excitement, which is due to lack of inhibition, the motor cells being actually weak. At such a time a peripheral impulse reaching the motor cell, instead of giving rise to a simple reflex action, and then

being inhibited, passes on and starts a series of reflex movements involving all the muscles and constituting a tetanic convulsion.*

The experiments of Lemattre indicate that belladonna exerts a similar paralyzant and convulsant action in mammals, and Fraser's investigation confirms this. (For details, see tenth edition.) It is very certain that in man atropine exerts this double influence; for the records of poisoning cases are at once the records of convulsions and of paralysis. It would seem that early profound paralysis occurs when a very large dose of the poison has been taken in a concentrated alkaloidal condition, and consequently has been rapidly absorbed and suddenly precipitated upon the nervous system.

Voluntary Muscles.—The voluntary muscles escape unscathed in atropine-poisoning. It is true that Lemattre has shown that the contractility of a striated muscle may be destroyed by soaking it in a very concentrated solution of the alkaloid; but long before any such action can take place in life the animal is killed; consequently after death from belladonna the contractility of the voluntary muscles is found unimpaired.

On the non-striated muscles the action of atropine is pronounced, but its exact nature is at present writing somewhat uncertain. It may, we believe, be considered proved that the toxic dose of atropine finally depresses all non-striated muscles; the original assertion of Bezold and Bloebaum, that this paralysis may become so complete that the strongest faradic currents are unable to cause movements either in the intestines, bladder, uterus, or ureters, being probably correct.

The uncertainty is as to the effects of small doses. P. Keuchel[13] seems to have proved that by a certain dose of atropine a condition is reached in which, although the peristaltic movements of the intestines are active, galvanism of the splanchnic—the inhibitory nerves of the intestinal coats—fails to have effect. If this be true, atropine paralyzes the peripheral inhibitory intestinal apparatus precisely as it does that of the heart. I. Ott[14] states that very minute doses of atropine prevent the production of peristalsis by salt placed upon the intestines, whilst large doses exaggerate the action of the salt. Admitting the correctness of the experiments of Ott and Keuchel, it is evident that atropine first stimulates the intestinal inhibitory nervous system and then paralyzes it. This, moreover, is corroborated by the fact that the smallest dose used by Keuchel was 0.075 grain, by Ott 0.015 grain, both observers experimenting on the rabbit. When Ott used 0.45 grain he got the same result as did Keuchel.

Respiration.—The medicinal dose of atropine ordinarily has no apparent effect upon the respiration; but both in man and in the lower

* The conjunction of excessive irritability with lack of power in motor cells is seen in very many diseased conditions, especially in hysteria. The fact discovered by H. C. Wood, that choreic movements in the dog are increased by atropine, fits very well the theory of the text. Choreic movements being the result of inhibitory weakness, the drug which further increases that inhibitory weakness should increase the movements.

animals the toxic dose usually, though not always, accelerates the respiratory movements. Researches upon the effect of atropine upon the respiratory movement* of air have been made by H. C. Wood,[15] Heubach,[16] E. Orlowski,[17] E. Vollmer,[18] and Unverricht.[19] The experiments of Heubach, Orlowski, Vollmer, and Unverricht were made upon animals under the influence of morphine; H. C. Wood's experiments were upon normal, morphinized, and chloralized dogs. The first effect of atropine in the normal animal is greatly to increase the respiratory air-movement. This primary excitement is usually soon followed by a decrease, which is not, however, sufficient to overcome the first rise; so that the air-movement remains for a long time distinctly above the normal. In the chloralized dog the effect of atropine in increasing air-movements is constant and pronounced. In H. C. Wood's experiments (two in number), as also in Orlowski's and Unverricht's, with animals under the influence of opium, no increase, but rather a decrease, in the air-movement was the result of injections of atropine. In Heubach's and in Vollmer's experiments, which were numerous, atropine distinctly increased the air-movement in the morphinized dog. The action of opium upon the respiration in the dog is at present so little understood that the question of the contra-action of atropine and morphine is entirely apart from that of the action of atropine. Atropine undoubtedly increases the respiratory air-movement, and as section of the vagi does not affect this action (Bezold and Bloebaum, *loc. cit.*, 59), atropine is a centric respiratory stimulant. It is probable, however, that the toxic dose of atropine affects respiration by paralyzing the peripheral pneumogastric nerve in the lungs, since in profound atropine-poisoning no marked influence is exerted upon the expiratory rhythm by section of the pneumogastrics.

Glandular System.—The suppression of the secretion of the mucous and salivary glands in the mouth and of the sudoriferous glands of the skin by atropine is almost certainly due to an influence either upon the peripheral nerve-filaments or upon the gland-cells themselves, since in Keuchel's experiments galvanization of the chorda tympani nerve was powerless to excite secretion in the atropinized parotid gland.

Small doses of atropine sometimes, but not always, increase the flow of urine. After the toxic dose the urine may be at first augmented, but is usually lessened very early, and may finally be entirely suppressed.† The assertion of Meuriot, that the urinary secretion rises and falls in atropine-poisoning with the arterial pressure, is not in accord with the results obtained by Walti,[20] who found atropine to produce in the rabbit, independently of its action upon the circulation, a steady lessening in the urinary secretion. Harley[21] affirms that medicinal doses of atropine decidedly increase the solids of the urine, slightly the urea and uric acid, very markedly the phosphates and the sulphates.

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* See *Respiratory Stimulants*, page 268.

† See case of Gross (*loc. cit.*), also of Morer (*Ann. Soc. de Méd. de Gand*, 1873).

Our knowledge of the action of atropine upon the secretions of the alimentary canal is very imperfect. It has been a matter of traditional and clinical belief that the secretions are increased, and Harley gives some experiments which he asserts corroborate this; Meuriot, on the other hand, states that they are lessened. We cannot find, however, any experiments that seem to us decisive; and clinical evidence certainly indicates that the intestinal secretions, if affected at all, are increased.

Temperature.—In moderate doses atropine causes a pronounced rise in temperature, but in very large decidedly toxic amounts it lessens animal heat. Thus, in the dog, Meuriot has obtained an augmentation of from 1° to 3° C., and Duméril, Demarquay, and Lecomte of 4° C. In fatal poisoning of the same animal, these observers have noticed a fall respectively of 5.10° and 3° C. In man, Meuriot, in the use of medicinal doses, has observed the temperature to rise 0.5° to 1.1° C., and Eulenburg 0.5° to 0.8° C. According to I. Ott and C. Collmar,[22] this increase is independent of the blood-pressure, occurring both when the pressure is elevated and when it is depressed, and is accompanied by a greater increase of heat-production than of heat-dissipation. It is therefore due to the increased heat-production, which is the result, in all probability, of an influence upon the nerve-centres. Ott and Collmar believe that this influence is a stimulation of the thermo-genetic centres in the spinal cord, and that the rise of temperature is paralleled by that which occurs in tetanus. It seems to us more probable that it is due to paralysis of thermo-genetic inhibition. The final fall of temperature in atropine-poisoning is probably, at least in part, caused by the vaso-motor paralysis.

Eye.—In all animals except birds, atropine causes mydriasis with paralysis of accommodation and probably lessening intra-ocular pressure.

The dilatation induced by the *local application* of atropine is not due to a direct action of the drug upon the muscular fibres of the iris; for as all of these, both the radiating and the circular, are of the same nature (*non-striated* in mammals), their antagonism is simply due to position; and it seems inconceivable that mere position should affect the relations between a muscle and a drug. Moreover, Bernstein and Dogiel (confirmed by G. Engelhardt) found that while galvanic irritation of the oculo-motor nerve was unable to cause contraction of the pupil in the atropinized eye, yet when the electrodes were applied to the eyes in such a way as to affect directly the iris, contraction occurred,—phenomena explainable only by the theory that the nerve-endings were paralyzed, while the muscle was unaffected.

The statement first made by Wharton Jones,[23] that the reason atropine does not dilate the pupils of birds is that their irides have no radiating fibres, has been disproved by the beautiful anatomical researches of Alex. Ivanoff and Alex. Rollett[24] (confirmed by Johannes Diegel[25]). Although Donders[26] says that the pupillary action of atropine "is slight in birds, in which it was formerly overlooked," in our own

experiments the most thorough application of very strong solutions to the eyes of pigeons has had no distinct effect. According to the experiments of Szpilman and Luchsinger, lack of action of atropine is probably due to the muscular fibres of the irides of birds being non-striated. In the œsophagus of the bird the muscle is non-striated, and atropine paralyzes it; in the œsophagus of the rabbit the muscle is striated, and atropine has no action; in the cat a portion of the œsophagus has smooth muscular fibres, a part striated, and the former is paralyzed, the latter unaffected, by atropine.[27]

The dilatation of the pupil by the local application of atropine* is certainly independent of any nerve-centres farther back than the ciliary ganglion.

This is proved by the following facts. Claude Bernard[28] and Lemattre both have found that atropine-mydriasis occurs in animals after section of the oculo-motor, and we have seen it in cases of complete oculo-motor paralysis in man. It also takes place after section of the trigeminus or of the cervical sympathetic, or of both of these nerves, as is shown by the testimony of numerous observers and by our own experiments. In man we have seen it after paralysis of the sympathetic.[29]

The dilatation of the pupil by the local application of atropine is independent not only of the central nervous system, but also of the ciliary ganglion, and is due to an action exerted directly upon the *nerve-endings in the iris.*

The experiments of Bernstein and Dogiel, confirmed by Engelhardt, already quoted, are in themselves almost enough to establish the truth of this proposition. More direct evidence is not, however, wanting. Thus, Vierordt† has found that atropine locally applied causes mydriasis after the removal of the ciliary ganglion. I. Hoppe[30] has discovered, and Y. Valentin[31] has confirmed the discovery, that in the eye of the frog removed from the body atropine will produce dilatation of the pupil. According to Borelli,[32] mydriasis is produced by the alkaloid when applied to the eye of a man just dead. Lastly, the presence of the alkaloid in the humors of the atropinized eye has been proved by numerous observers, among whom may be mentioned Lemattre and Donders, who have found that the liquids removed from such an eye are capable of causing dilatation of the pupil of another eye.

The dilatation is, at least in part, due to paralysis of the peripheral filaments of the oculo-motor nerve. Both Donders and Stellwag von Carion[33] insist that the paralysis of accommodation is proof of paralysis of the oculo-motor nerve, and it seems to us they do so with truth. However this may be, there is abundant direct proof that the oculo-motor fibres are paralyzed, since the experiments of Grünhagen, which prove that galvanization of the exposed oculo-motor nerve does not

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* Contraction of the pupil before dilatation noticed in dogs (Reese) and rabbits (Rossbach and Fröhlich) is probably caused reflexly by the irritant action of the atropine.

† Unfortunately, the only notice we have seen of this capital experiment is in Hermann's *Grundriss der Physiologie.* No reference is given, and we have been unable to find the original paper.

affect the atropinized pupil, have been confirmed by Engelhardt[34] and by Rossbach and Fröhlich.[35]

It is probable that the sympathetic or dilating nerve-fibres of the iris are stimulated.

Clinical experience certainly shows that the dilatation produced by a mydriatic is not merely a passive movement of relaxation, but is active, capable of tearing up inflammatory adhesions even when of some firmness. Again, the dilatation that occurs after the paralysis of the oculo-motor nerve in man and after its destruction in animals is not at all equal to that produced by atropine, and, indeed, can be largely increased by the action of the drug; further, in the eye separated entirely from the nerve-centres (see above) atropine still causes a wide dilatation; facts which necessitate the belief either that the alkaloid acts upon the sympathetic fibrillæ or that the peripheral fibres of a nerve are in themselves nerve-centres, acting upon the muscle of themselves even when separated from their centres. It has been urged against the view here taken that even the widest artificial mydriasis is increased by galvanization of the sympathetic. De Ruiter states the contrary; but, since Grünhagen, Hirschmann, and Engelhardt separately affirm as the result of personal experiment the correctness of the asserted fact, it must be accepted. Granting its truth, we do not think it warrants the deduction, since it is conceivable that an agent may excite the peripheral filaments of a nerve greatly, and yet not to such a point that they will be incapable of further excitation.

A priori, it is strongly to be expected that the action of atropine upon the pupil will be the same whether it is carried to the pupil by the blood or is applied locally by the surgeon. The correctness of this conclusion is shown by the following evidence. Lemattre asserts that he has secured mydriasis in normal eyes by placing in them aqueous humors taken from dogs poisoned with atropine; others, however, have failed to get the dilatation. It has been asserted by authorities, and experimentally corroborated by H. C. Wood, that atropine given hypodermically caused dilatation of the pupil in the lower animals after section both of the trigeminus within the skull and of the sympathetic in the neck; H. C. Wood has shown that this also occurs after such section of the parts behind the eye up to the optic nerve as secures complete isolation of the iris from any nerve-centre. What is true of the lower animals is also true of man; accident having afforded H. C. Wood the opportunity to give atropine hypodermically to a man whose eye had been separated from all connection with the nerve-centres, it was found that the pupil was still dilated by the drug.*

Our knowledge of the action of atropine upon the pupil may be summed up as follows. Atropine applied locally causes mydriasis by paralyzing the peripheral ends of the oculo-motor nerve, and probably by stimulating the peripheral ends of the sympathetic. Atropine given internally causes mydriasis, not by influencing the nerve-centres, but by being carried in the blood to the eye itself and there acting precisely as when applied locally.

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* For elaboration of details, see tenth edition of this book.

SUMMARY.—In full medicinal doses atropine produces a sort of febrile state, with dryness of the mouth, dilatation of the pupil, increased rapidity and force of the circulation, quickened respiration, elevation of temperature, and secretion of febrile urine. The toxic dose intensifies the symptoms just narrated, and adds to them a peculiar wild delirium. The stage of excitement may be many hours long, with very rapid heart-action and high arterial pressure; after a time it is followed by one of general functional failure, marked by stupor, fall of blood-pressure, depression of reflexes, and death from asphyxia. The cerebral symptoms are due to direct influence of the alkaloid upon the cerebral cortex. The primary increase of respiration is the outcome of centric stimulation; the terminal depression and asphyxia are produced by secondary depression of the respiratory centre, and especially by depression of the respiratory nerves. Upon the spinal cord the therapeutic dose probably has no influence, but the toxic dose acts as a depressant, affecting, however, more powerfully the motor nerve-trunks than it does the spinal centre and to a less degree the sensory nerves. There is some reason for suspecting that the drug primarily acts as a feeble stimulant to the various inhibitory centres, but its pronounced characteristic effect is that of a paralyzant of peripheral inhibition, acting in this way upon the spinal cord itself, upon the pneumogastric nerve, and upon the splanchnics so as to increase intestinal peristalsis. The rapid pulse is chiefly the outcome of a paralyzed inhibition, although the heart may be feebly stimulated. The primary rise of blood-pressure produced is chiefly due to stimulation of the vaso-motor centres, although probably the work of the heart itself is increased. The final fall of pressure is due to depression of the heart and of the muscular coats of the vessels, which is part of a general action upon non-striated muscle-fibres, and which results in suspension of intestinal peristalsis and in retention of urine.

THERAPEUTICS.—In practical medicine atropine is employed in direct conformity to its physiological action, so that its use is best discussed under the headings of the various indications to meet which it may be administered.

To relax Spasm.—As the powers of atropine to relax spasm depend on its influence upon the peripheral nerve-filaments and the muscle-tissue, it is evident that it is a practical remedy only in those cases in which the spasm is due to some local cause connected with a muscle or its supplying nerve; hence it has been found especially useful in *rheumatic torticollis*, in the violent contractures and spasms sometimes accompanying *neuritis*, and especially such as follow *nerve-wounds*. It is essential to inject the alkaloid directly into the contracted muscle, so as to get its concentrated influence upon the affected nerve and muscle, little or no relief usually being produced by so small an amount of the remedy as would reach the diseased part after absorption through the blood. The non-striated muscles are more affected by the atropine than the striated, and consequently the drug is found to be more efficacious in spasm of the involuntary than of the voluntary muscles. It is serviceable in *lead colic*, in *simple spasmodic colic*, in *spasmodic dysmenorrhœa*, in *spasmodic constriction* of the *bowels* with *obstinate constipation*, in *laryn-*

gismus stridulus, in *nervous cough*, in *asthma*, in *hiccough*, and in *whooping-cough*, in which last disease, as originally advised by Bretonneau, it has been largely used; also, even in the spasms accompanying the passage of *renal* and *biliary calculi*, where of course it usually fails. Wherever it is possible, it should be used locally in spasm of the involuntary as well as of the voluntary muscles. Thus, in *spasm* of the *urethra*, the ointment should be rubbed in along the canal; in *rigid os uteri*, the extract should be applied directly to the os; in *asthma*, belladonna should be inhaled, by means either of the cigarette or of the atomization of a decoction of the leaves; in *spasm* of the *sphincter ani* from *fissure* or other cause, it should be applied directly to the part by poultice or ointment. Under the present indication may be considered the use of the remedy in *constipation*. In doses of one-quarter to one-half grain of the extract, belladonna is of great service as an addition to laxative pills. In that form of *incontinence of urine* in children in which the real cause is an irritability of the bladder, so that spasmodic contraction occurs under the stimulus of a small portion of urine, the continuous use of large doses of atropine is often of great service by reducing the irritability of the walls of the bladder, with which, owing to the method of its excretion, the alkaloid is brought in local contact.

To relieve Pain.—In accordance with its known physiological action, atropine is of very little value for the purpose of relieving pain, unless such pain be connected with spasm, or unless the pain be due to ulceration or other local cause so situated that the atropine can be brought in direct contact in concentrated form with sensory nerve-endings.

To impress the Heart and Blood-Vessels.—In certain diseases, such as *pneumonia*, *congestion of the lungs*, etc., in which the local affection is closely connected with dilatation of the blood-vessels, Harley has highly commended atropine as a vaso-motor contractant. In most of these affections, however, the remedy has failed to establish itself. In acute *coryza* and *angina* it acts most favorably, its influence upon the circulation being probably supported by its specific action upon the glandular apparatus of the mucous membranes involved, and possibly by its relaxing the pharyngeal muscles.

As a stimulant to the circulation, belladonna has probably not been employed as much as it ought. Graves, however, commends it especially when the pupil is contracted in *typhus fever*, and it has been used with asserted advantage in *erysipelas*, *scarlet fever*, etc. In cases of sudden *collapse* occurring in acute disease and marked by falling of the temperature below normal, with great loss of the arterial tension and free sweating, atropine is of the greatest value. Such collapse is not infrequent in young children in the advanced stages of *pneumonia*, *pleurisy*, or other pulmonic disease, and is also prone to happen in puerperal *mania* and similar maniacal states occurring in exhausted patients. It is similar in its character to that which is produced by perforations of the stomach or intestine or as the result of surgical or accidental traumatisms. It is a

condition of *shock* in which the loss of temperature is chiefly the result of vaso-motor paralysis. Proper treatment of this condition consists chiefly in the free use of external heat and the hypodermic injection of atropine, strychnine, and the tincture of digitalis ; in many of these cases alcoholic stimulants are worse than useless.

To arrest Secretion.—In *mercurial salivation* atropine arrests almost at once the discharge of saliva, and seemingly facilitates greatly the return to health. In *colliquative sweats*, as originally recommended by Da Costa,[36] it is probably the most valuable known remedy. One-sixtieth to one-eightieth of a grain of atropine used hypodermically, at bedtime, will very frequently prevent the usual *night-sweat*. In *colliquative diarrhœa* it has been recommended by M. Delpage, and very probably will be found of service. Inunctions of the breast with belladonna ointment are habitually employed for the purpose of arresting the secretion of milk, and in the experiments of Hammerbacher[37] upon a goat, atropine given internally lessened the secretion, especially of the watery portions of the milk.

Employment in Poisoning.—It is stated that as far back as 1570 it was affirmed that opium and belladonna are, in their influence upon the system, antagonistic. In the early part of the present century their employment as counter-poisons was again brought prominently before the profession ; but, although a few scattered earlier records of their use as such exist in medical literature, it was not until the paper of William F. Norris[38] appeared that general attention was attracted to the subject. After nearly twenty-five years of discussion,* the opinion given in the first edition of this work, that the two drugs are not, strictly speaking, antagonistic, has become a certainty. Atropine, is, however, a valuable remedy in opium-poisoning as a powerful and prompt respiratory stimulant. In protracted opium-narcosis the cardiac and vaso-motor actions of atropine are of service ; but it should never be forgotten that the main influence for good is upon the respiratory centres. The first improvement from atropine in these cases is usually increased frequency of respiration ; and as the breathing becomes less embarrassed the other symptoms ameliorate, largely because of the increased aëration of the blood.

The double nature of profound opium-narcosis must not be lost sight of : the blood is saturated with carbonic acid almost to the dead-line, and much of the unconsciousness, much of the failing circulation, much even of the embarrassed respiration, is due to the presence of the gas. As soon as the system is in a measure relieved of this load, it begins to rebound ; emetics act, consciousness returns to some extent, the circulation frees itself, and the road leading towards health is entered upon. Atropine should be administered as soon as there is decided failure of the respiration. With it should be given strychnine, which, as was first pointed out by H. C. Wood, is at least equally as efficient as atropine. Both alkaloids

* For an account of this discussion, see tenth edition of this treatise.

should be given hypodermically, the doses being large but not toxic : one-fortieth of a grain of atropine and one-fifteenth of strychnine are, in most instances, fair commencing doses. Repetition should be chiefly guided by the effect upon the respiration, although judgment should be formed in part from a bird's-eye view of the whole case. No more of the alkaloids should be used than is necessary to sustain the respiration ; so long as this function is improving they should be withheld.

Whenever there is failure of respiration in other poisonings than that of opium, atropine in conjunction with strychnine is useful. It has been especially commended as an antidote to *poisonous fungi.**

As a Local Sedative.—Locally and freely applied, belladonna is a sedative, and, we believe, to glandular as well as to muscular and nervous tissues. In this way it is often very useful in various local inflammations. In the form of a plaster it frequently appears to do good in *palpitation of the heart.* Its use locally in spasms and in neuralgia has been sufficiently dwelt on. In *mastitis*, its local application to the breast is often very efficacious. Whenever belladonna is used locally, in order to get its good effects it must be employed freely. At the same time, it should be remembered that a number of cases of poisoning by its external application have been reported.[39, 40] In children it must be used with caution ; in adults, with a reasonable amount of care, its external use is safe, provided directions be given to have it washed off so soon as any affection of the sight or dryness of the throat is induced.

Use in Diseases of the Eye.—The instillation of a four-grain solution of atropine sulphate into the eye is followed in about fifteen minutes by dilatation of the pupil, usually reaching its maximum in twenty-five to thirty-five minutes, and lasting until the third day. In about twenty-five minutes the power of accommodation begins to be lost, and in an hour and a half to two hours is usually fully annulled : return begins on the second day, but the function may not be fully regained for over a week.

Atropine is used by ophthalmologists : first, to dilate the pupil for the purposes of ophthalmoscopy, but is inferior to more rapidly and fugaciously acting mydriatics : second, in *iritis*, to keep the pupil from being contracted by exudates, to give rest to the iris, and to prevent the development of extensive synechiæ ; for this purpose it is probably the best of the mydriatics : third, to expose the lens in cases of incipient *cataract*, so that all portions of it may be carefully examined : fourth, to paralyze accommodation, when it is desired to determine with accuracy the refraction of the eye for the fitting of spectacles or other purposes ; in such cases repeated instillation of atropine may be necessary : fifth, to give rest to the eye and exert an anodyne alterative influence in all inflammation of the cornea ; in *phlyctenular keratitis* it is especially useful, and in perforating *ulcers* may overcome the prolapse of the iris ; for this purpose it must be used very freely.

* Atropine antagonizes the action of muscarine (the alkaloid of many of the poisonous mushrooms) on the cardiac inhibitors as well as on the respiration.

The existence of *glaucoma*, or any tendency to it, is a contra-indication to the use of atropine. It may in chronic glaucoma precipitate an acute attack, and in acute glaucoma causes marked increase of pain, of congestion, and of the already excessive intra-ocular tension.

Belladonna was at one time highly commended as a prophylactic against *scarlet fever*. The original teaching of George B. Wood, that as such, however, it has no value, has been abundantly confirmed in later times.

TOXICOLOGY.—Sufficient has already been said about the general symptoms of belladonna-poisoning. Those which are characteristic are the dryness of the throat, the increased frequency of breathing, the dilated pupils, the red efflorescence on the skin, the rapid pulse, the active talkative delirium, sometimes convulsions, all ending in abolition of function, as shown by stupor, rapid feeble pulse, cold extremities, and paralysis. Morel [41] calls attention to a sort of laryngitis produced by poisonous doses of belladonna, characterized by pain in the larynx, roughness of voice, and the expectoration of minute, pearly, tough pellets. It was present in the advanced stages of two cases of poisoning under his care.

The minimum fatal doses of the preparations of belladonna are scarcely known.

An enema representing eighty grains of the root has produced death in five hours ;[42] but, on the other hand, recovery has occurred after the ingestion of three drachms of the extract.* A tenth, or even a twentieth, of a grain of atropine will often produce alarming symptoms ; yet Chambers [43] reports recovery in a child four years old who had taken about two teaspoonfuls of a solution containing a grain of the alkaloid in half an ounce.

After death from belladonna, no characteristic lesions are to be found.

In the treatment of belladonna-poisoning, the stomach should be emptied by means of emetics or the stomach-pump, and tannic acid exhibited as an imperfect antidote. The various symptoms must then be met as they arise, respiration and circulation being maintained as in other narcotic poisoning. The exact value of opium in belladonna-poisoning has not been determined, and its employment should be tentative, although good is to be expected from its judicious use. Physostigma and jaborandi appear to be somewhat antagonistic to atropine within certain limits, and jaborandi has been used in atropine-poisoning. (See Calabar Bean and Jaborandi.) After toxic doses of belladonna, there is generally complete retention of urine ; and as this secretion contains the greater part of the ingested poison, and as reabsorption from the bladder is at least conceivable, the catheter should be used early.

ADMINISTRATION.—Belladonna is never used internally in substance. All the preparations of the U. S. Pharmacopœia except two (designated below) are made from the leaves. They are the tincture (TINCTURA

* Taylor's *Medical Jurisprudence*, London, 1873, 432.

BELLADONNÆ FOLIORUM—fifteen per cent., U. S.), dose, ten to thirty minims (0.6–1.9 C.c.); the alcoholic extract (EXTRACTUM BELLADONNÆ FOLIORUM ALCOHOLICUM, U. S.), dose, one-eighth to one-half grain (0.008–0.032 Gm.); the fluid extract of the root (EXTRACTUM BELLADONNÆ RADICIS FLUIDUM, U. S.), dose, one to two minims (0.06–0.12 C.c.); the plaster (EMPLASTRUM BELLADONNÆ, U. S.*) representing its weight of root; the ointment (UNGUENTUM BELLADONNÆ, U. S.) containing ten per cent. of extract. The liniment (LINIMENTUM BELLADONNÆ, U. S.) is made by adding five per cent. of camphor to the fluid extract. Atropine sulphate (ATROPINÆ SULPHAS, U. S.) is most commonly used, on account of its solubility in water. Dose, one-hundredth to one-sixtieth of a grain (0.00065–0.001 Gm.), increased in cases of poisoning. In dropping an atropine solution in the eye for local effect the head should be so inclined that the fluid will run out of the outer canthus, whilst pressure may be applied upon the optic end of the lachrymal duct to prevent passage of the solution into the mouth. Poisoning through the local use of the remedy by ophthalmic surgeons has often occurred.

HOMATROPINE HYDROBROMATE.—Homatropine is an alkaloid artificially produced from atropine, the *hydrobromate* of which is preferred for practical use on account of its being stable and not hygroscopic. It is said to cause, when taken internally, symptoms similar to those caused by atropine, except in regard to the circulation. The retardation of the pulse has been proved by Tweedy and Ringer, Beyer, and De Schweinitz and Hare[1] to be, at least in part, the result of a direct action of the drug upon the heart-muscle or its contained ganglia, since in the frog and in the terrapin the application of homatropine hydrobromate to the exposed heart *in situ* reduces very greatly the number of the beats. In the dog injection of the alkaloid into the jugular vein is followed by a fall of as much as thirty or forty beats per minute, which De Schweinitz and Hare believe to be in part due to stimulation of the vagi nerves, because section of the vagi causes a marked increase in the pulse-rate, "although not such a rise as would appear if the inhibitory apparatus was intact." De Schweinitz and Hare found that the fall of the pulse-rate was accompanied by a marked fall of the arterial pressure. Since the production of asphyxia was followed at this time by a pronounced rise in the arterial pressure, it would appear that the fall of pressure is not the result of a vaso-motor paralysis, but of the cardiac influence of the drug.

It has been shown by the experiments of Tweedy and Ringer, confirmed by De Schweinitz and Hare, that homatropine produces in the frog a brief period of tetanus, followed by absolute muscular relaxation,

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* Constitutional symptoms are readily produced by the free external use of belladonna plaster or ointment; and patients should always be warned to remove the plaster if dryness of throat or disorder of vision come on. For cases of poisoning in this way, see *N. Y. Med. Record*, Jan. 1884, also *Journ. Amer. Med. Assoc.*, ii. 122.

with abolition of reflex and voluntary activity, followed in from six to eight hours, if the dose has been properly proportioned, by return of voluntary movements, associated with tetanic spasms of great intensity. The convulsive movements and the paralysis are, according to De Schweinitz and Hare, of spinal origin, as the nerve-trunks and muscles are not affected. The cause of death is centric respiratory paralysis.

The influence of the alkaloid upon the eye is practically identical with that of atropine, except that it is somewhat more feeble and is much more temporary. The pupil begins to dilate in from seven to twenty minutes after the instillation of the drug, and accommodation fails in from forty to ninety minutes; in from one to seventy-two hours the recovery is complete. According to De Schweinitz, a solution of one in eighty is sufficiently strong to paralyze accommodation completely, provided it be dropped repeatedly into the eye. When it is desired simply to dilate the pupil for ophthalmoscopic examinations, a single application of a solution of four grains to the ounce suffices. Homatropine as a practical mydriatic has the advantage of fugaciousness of action, of being not at all irritant, and of being little prone to produce systemic disturbance.

STRAMONII FOLIA—STRAMONIUM LEAVES. U.S.
STRAMONII SEMEN—STRAMONIUM SEED. U.S.

The leaves and seeds respectively of the Datura Stramonium, or *Jamestown Weed*, a coarse, bushy, annual herb, three or four feet high, growing in waste places both in this country and in Great Britain, and readily distinguished by its large, funnel-shaped, whitish, fetid flowers, and its quadrivalve spinescent capsules. The leaves are large, smooth, ovate, irregularly sinuate, with large acute teeth. The seeds are small, brownish black, reniform, with a bitterish narcotic taste. The alleged active principle, *Daturine*, is, according to Ladenburg, a mixture of atropine and hyoscyamine.

Physiological Action.—The symptoms of poisoning by stramonium differ in no respect from those of belladonna-poisoning, although Laurent[1] asserts that irregularity of the heart's action is more marked under the influence of stramonium. The same accelerated pulse, the same elevation of temperature, the same wild delirium, the same increased frequency of respiration, the same widely dilated pupils, the same red efflorescence on the skin, the same restlessness or convulsions, occur in both cases, and, when the dose has been sufficiently large, end alike in abolition of the functions of circulation, respiration, and innervation,—stupor, general paralysis, weak, rapid, thready pulse, and threatened asphyxia constituting the phenomena of the closing scene in poisoning from either narcotic.

Charles Laurent found that under the microscope the capillaries of the frog's web could be seen to contract upon the application of daturine, even after division of the nerves of the limb; that the pulse-rate and arterial tension are both augmented by small doses of the poison, but

that by large doses the arterial tension is diminished, although the pulse is still increased in frequency ; that when the heart is completely separated from all connection with the central nervous system, daturine reduces the number of its beats ; that respiration is accelerated, even after section of the pneumogastrics ; that by moderate doses the conducting power of the sensory or of the motor nerves is not destroyed ; that the muscular contractility is not affected ; that small doses increase, large ones diminish, intestinal peristalsis. Elaborate discussion of these facts seems unnecessary. The physiological action of *daturine* is not to be distinguished from that of *atropine*.

THERAPEUTICS.—Stramonium may be used to meet precisely the same indications as belladonna. It has been especially employed in spasmodic *asthma*, chiefly in the form of cigarettes made by rolling up the dried leaves. These are often very efficient when there is no organic disease ; but their use requires some caution, as very alarming symptoms, if not fatal results, have been produced by them. In the form of cataplasms, stramonium leaves are often applied with advantage to painful *local inflammations*, *inflamed hemorrhoids*, etc.

ADMINISTRATION.—The official preparations of stramonium are all made from the seeds. They are the extract (EXTRACTUM STRAMONII SEMINIS, U. S.), dose, one-fourth to one-half grain (0.016–0.032 Gm.) ; the tincture (TINCTURA STRAMONII SEMINIS—fifteen per cent., U. S.), dose, ten to twenty minims (0.6–1.2 C.c.) ; the fluid extract (EXTRACTUM STRAMONII SEMINIS FLUIDUM, U. S.), dose, one to two minims (0.06–0.12 C.c.) ; and the ointment (UNGUENTUM STRAMONII, U. S.), containing ten per cent. of the extract.

TOXICOLOGY.—Accidental poisoning, especially of children, by stramonium, is very common. In all points, as regards both symptoms and treatment, stramonium-poisoning and belladonna-poisoning are alike.

HYOSCYAMUS. U.S.

Hyoscyamus niger is a coarse herbaceous biennial, indigenous in England, and naturalized in the Northern United States, whose leaves and flowering tops of the second year's growth are official. The leaves are large, oblong-ovate, deeply sinuated, and very hairy. Hyoscyamus contains two alkaloids : one is crystallizable, constitutes the crystalline hyoscyamine of commerce, and its sulphate is the HYOSCYAMINÆ SULPHAS of the U. S. Pharmacopœia ; the other is amorphous, constitutes the amorphous hyoscyamine of commerce, and in its pure state is *Hyoscine* (see page 138). Its salts are crystallizable.

PHYSIOLOGICAL ACTION.—Both Schroff and Düllenberg have noticed in man, as the result of the ingestion of hyoscyamus, dryness of the throat and mouth, brief sinking of the pulse-rate, followed by increased frequency, mydriasis, giddiness, muscular weakness, and insecurity of gait. The experiments of Schroff, of Laurent, and especially of Harley[1] indicate that hyoscyamus is much more of an hypnotic than is belladonna.

Yet Harley's recorded observations would seem to show that in some individuals hyoscyamus induces insomnia. According to Harley, the primary sinking of the pulse is much more marked after hyoscyamus than after belladonna. Laurent[2] affirms that the delirium caused by hyoscyamus is calm, while that produced by belladonna is furious; but on page 19 of his book is recorded a case of henbane-poisoning in which the delirium was "furious." Schroff[3] asserted that pneumonia is a constant and even characteristic lesion of hyoscyamus-poisoning in the rabbit; but Lemattre has never seen more than little scattered points of hyperæmia; and in Laurent's experience even these have always been absent.

According to the elaborate experiments of Laurent, hyoscyamus acts very similarly to belladonna upon the circulation, the respiration, the nervous system, the muscles, and the intestines. The more important of these conclusions were also experimentally arrived at by Heilmann.[4] R. Gnauck[5] found that hyoscyamine agrees with atropine in its action upon the vagus and heart-muscle, but is less powerful and persistent in its influence, and also acts as a powerful soporific: it further appeared especially to dilate the internal abdominal vessels.

THERAPEUTICS.—Hyoscyamus may be used to fulfil any of the indications for which belladonna is employed. Clinical experience appears in a measure to bear out the assertions of various authorities as to the superiority of hyoscyamus as an hypnotic. It has been much employed as a calmative and hypnotic by alienists in various forms of delirious *insanity*, but is inferior to hyoscine. The diagnosis and treatment of hyoscyamus-poisoning are identical with those of belladonna-poisoning.

The preparations are the extract (EXTRACTUM HYOSCYAMI, U. S.), dose, one to three grains (0.06–0.19 Gm.); the tincture (TINCTURA HYOSCYAMI—fifteen per cent., U. S.), dose, half a fluidrachm to two fluidrachms (2–8 C.c.); and the fluid extract (EXTRACTUM HYOSCYAMI FLUIDUM, U. S.), dose, five minims (0.3 C.c.).

HYOSCYAMINÆ SULPHAS. U. S.—*Hyoscyamine sulphate* is a whitish powder, sometimes indistinctly crystalline, very soluble in water, and having a bitter taste. According to J. C. Shaw,[6] crystallized hyoscyamine affects the system of voluntary movement and the circulation, including the heart and the vaso-motor system, exactly as atropine does. In a single experiment the respiration did not seem to be affected as by atropine; but this is contradicted by results arrived at by previous experimenters, and needs confirmation. Upon man Shaw believes, as do many other alienists, that hyoscyamine acts as a soporific. He states that it is less powerful as a mydriatic than is atropine, and that it diminishes the respiratory rate. It must be remembered that these studies have been made upon lunatics; before the conclusions can be accepted as established, much more elaborate experimental researches are necessary, also studies upon normal individuals, and especially contrasting studies made

with atropine and hyoscyamine upon maniacs ; by the use of alternate doses upon the same individual any difference of action of the two drugs could readily be detected. It should also be remembered that in his studies of hyoscyamine upon normal men Richter[7] noted no tendency to sleep. In a careful comparative study of hyoscyamine and atropine upon a case of acute mania by Sydney Ringer,[8] the two alkaloids were found to act practically alike. Commercial hyoscyamine was formerly very impure, and a grain has been given with impunity ; but one-fortieth of a grain of the pure alkaloid has produced violent poisoning.[9]

COCA. U.S.

The leaves of Erythroxylon Coca, a South American shrub, which is very largely cultivated in Peru and neighboring countries, resemble in size and shape those of tea, but are not dentate, and are distinguished from most medicinal leaves by a slightly curved line, running from the base to the apex, on each side of the midrib, and produced by the peculiar folding of the leaf in the bud. In 1855 Gardeke discovered in coca an alkaloid to which he gave the name *Erythroxyline ;* but this principle was first thoroughly studied by Albert Niemann, from whom it received the name *Cocaine*, by which it is now usually known. It occurs in colorless, transparent prisms, soluble in seven hundred and four parts of cold water, and forms with the acids very bitter, soluble, crystallizable salts ; besides cocaine, the leaves contain a peculiar tannin, known as *coca-tannic acid.*

Physiological Action.—*Local Action.*—Locally applied, cocaine acts as a very distinct and certain anæsthetic, as was noted by Moreno y Maiz in 1862, and by Von Anrep in 1880, although it was not until September, 1884, that Karl Koller[1] demonstrated the practical value of the drug. According to the observations of Von Anrep, the nerves of special sense are as readily affected as are those of common sensibility : thus, cocaine placed upon the tongue abolishes at the place of contact, for the time being, the sense of taste. At the point of contact there is at first marked pallor, but after a short time very pronounced redness. In sensitive membranes like the conjunctiva, cocaine also causes at first much pain. The primary pallor is alleged to be due to a very powerful constriction of the small blood-vessels, and has led F. H. Bosworth[2] to the conclusion that cocaine produces *rigid contraction in unstriped muscular fibres* whenever it comes in contact with them. The anæsthesia is not, however, due to any spasm of the vessels, but to a direct action upon the nerve-trunk. Applied to the bared nerve, cocaine paralyzes first the sensitive and afterwards the motor fibres (Feinberg[3]). Arloing[4] asserts that the concentrated solution of cocaine placed on the bared nerve produces a distinct organic change in the nerve.

According to the experiments of Peter Albertoni[5] and of B. Danilewsky,[6] cocaine in sufficient concentration acts upon all forms of protoplasm, first exciting and then paralyzing functional activity.

Absorption and Elimination.—The soluble salts of cocaine are absorbed with great rapidity. They have the power of passing with almost equal ease through all mucous membranes, so that their absorption is almost immediate when they are employed locally in the nose, urethra, or other part ; hence the large number of serious poisonings which have resulted from their local use. They probably escape with most of the excretions from the body, but appear only to have been detected in the urine (Thomas Moreno y Maiz[7]).

General Action.—From the days of the Incas the leaves of the coca plant have been enormously used by the natives of Western South America as a stimulant, and it is stated that about forty million pounds of them are annually harvested. Mixed with ashes or a little lime, they are chewed, and are said to increase greatly for the time being the muscular strength and endurance. Although coca is thus employed habitually, no scientific observers have given detailed reports of the symptoms which it causes in the South American natives, observers contenting themselves with the mere statement that the physical and mental powers of the natives are greatly stimulated by the drug. Moderate doses appear to increase temporarily, to a very extraordinary degree, both physical and mental power. Various travellers concur in praising the peculiar sense of calm and happiness, the insensibility to fatigue, and the increase of bodily and mental activity which the drug produces.

Montegazza states that when he took two hundred grains of the leaves he was in a short time plunged into a condition of peculiar delirious beatitude, in which he seemed to be isolated from the rest of the world and to live in a peculiar atmosphere of active calm. In a little while there came also a sense of plenitude of power which was accompanied by a real increase of physical ability, so that gymnastics which in his ordinary condition were impossible to him became easy. This state was succeeded by a natural profound sleep, lasting sometimes for twenty-four hours.

Thus, on one occasion Montegazza took thirty-five grammes, and an hour later nine grammes, etc., until he had taken in the course of two hours sixty grammes in all. The heart, which after the earliest dose had been slow in its action, directly after the second dose suddenly became rapid and very violent in its beats; but at the end of the two hours the palpitations had ceased, although the pulse was still 128 per minute. There was now a condition of intoxication similar to that which is produced by hashish. Montegazza was possessed by a feeling of intense beatitude and inner joyousness, while a succession of visions and phantasmagoria, most brilliant in color and form, trooped rapidly before his eyes. He seemed to himself to look upon a world of shifting and incessant activity, as into a kaleidoscope. He rapidly passed into a delirious condition, in which he appeared to himself to be unconscious, although when addressed he would answer rationally. To his own consciousness he was, as it were, buried in a revery, or perhaps a more accurate description would be to say that he felt as though, by a sudden rush of intellectual and emotional life, he was carried out of himself, and knew not whether he was in or out of the body. An hour or two later he was sufficiently calm to say to his friends "that God was unjust, in that he had made man

to live without eating coca. I prefer a life of ten years of coca to one of a thousand years without it." As this state was passing off, he was seized with an almost irresistible desire to reproduce its delirium by taking more coca. Finally, however, he fell into a condition of sleep, which lasted only three hours. After this he was able to resume at once his ordinary occupations, and offered no physical evidence of his coca debauch.

The moderate daily use of coca, according to our best information, is not injurious, and increases the working powers; but, according to Poeppig, the habit of excessive use is readily formed, and produces very serious results. The first symptoms are usually those of disorder of the digestive organs. Little by little the power of digestion is lost; an incurable insomnia is developed, emaciation becomes extreme, ascites appears, and the patient finally dies in a condition of general marasmus. Other authors especially dwell upon the enfeeblement of the intellectual faculties as very marked in those who use the stimulant to excess. Tschudy states that the inveterate coca-chewer can be recognized by his uncertain step, his general apathy, his sunken eyes surrounded by a deep purple aureole, his trembling lips, his green encrusted teeth, his excessively fetid breath, and the peculiar blackness about the corners of the mouth.

Pronounced aphrodisiac properties have been attributed to coca, but they seem to rest upon tradition rather than upon demonstrated experience. According to M. Unanne, the ancient inhabitants of Peru represented Venus by a female figure with a coca-leaf in her hand, and the coca still plays an important part in the nuptial ceremonies of the Indians.

It has been affirmed by Tschudy and Unanne that coca is able to take the place of food; but this is clearly not the case. Weddell himself states that although an Indian chewing the coca could go on foot many hours without fatigue and without food, yet at the end he would eat more at one repast than he himself would take in two days. He accords with Bibra[8] in stating that coca has the power of putting aside for some time the sense of hunger. While, however, it may mask the appetite, it certainly does not nourish the body, and it is indeed most probable that the absence of hunger is the outcome of a local benumbing of the gastric nerves. Thomas Moreno y Maiz made several crucial experiments by keeping animals in pairs without food, and giving to one coca freely. These experiments have been repeated by B. von Anrep,[9] and in every case the animal which received the coca died at least as early as its mate.

The symptoms which have been present in cocaine-poisoning, or have been produced by the coca-leaf or its preparations, in the United States or in Europe, differ essentially from the descriptions of those said to be caused by the plant in the South American natives.* We believe that in

* The belief of H. H. Rusby, that these differences depend upon alterations of the coca-leaf during its drying and transmission across the seas, has hardly been sustained (*Therap. Gaz.*, 1888).

no recorded cases has there been anything resembling the beatific visions and exhilarations described by Montegazza. Ordinarily, in the mildest cases of poisoning with us, there are great restlessness and nervous excitement, but no sense of beatitude; rather a condition of terror. With this state come usually distinctly accelerated pulse, increased frequency of respiration, and, perchance, muscular twitchings or even mild convulsions. In the more severe cases of poisoning the symptoms vary; sometimes there have been nausea, vomiting, rapid, almost imperceptible pulse, great perspiration, and collapse with or without loss of consciousness; in other cases the pulse has been slow and feeble, and sometimes pronounced cyanosis, with slow or almost arrested respiration, has been the most alarming manifestation. The pupils are usually dilated, but have been reported in some cases as "contracted." After very large doses convulsions usually oocur; they are often violent and epileptiform; not rarely, at times, at least, they are partial, and in many cases opisthotonos has been pronounced. Consciousness rarely escapes; usually it is simply lost, but sometimes it is merged into a mania with hallucinations and delusions, which mania may become violent and even homicidal, as in a case reported by Mattison.

Very small doses (one- to three-one-hundredths of a grain of cocaine) produce in the frog no other symptoms than some evidences of excitement. After doses of from one-tenth to one-fiftieth of a grain the frog becomes quiet, with an apparent increase, however, in the reflex activity, sometimes amounting to tetanus, followed by increasing palsy and failure of the respiration; very large doses produce symptoms of paralysis.

In the domestic animals the symptoms vary. In the rabbit there is first a peculiar state of quiet, followed in a few moments by a condition of great excitement, in which the animal springs and jumps about. A few minutes later the rabbit again becomes quiet, and now, although trembling much, is so weak that he moves with difficulty. The tremblings increase until they merge in convulsive movements of the legs, while at the same time there is partial paraplegia; pendulum movements of the head are very marked, and finally epileptiform convulsions appear, while simultaneously a peculiar tetanic rigidity seems to indicate spinal excitement. The lethal dose for a rabbit is put at a grain and a half per kilo. Dogs and cats are said to be more susceptible to the action of cocaine than is the rabbit, and to suffer similar symptoms, but especially with the dog the evidences of mental excitement are more pronounced.

According to Von Anrep, after an injection of cocaine the dog will dance and leap, never standing still for a moment, and continually circling around the experimenter. The movements are not at all those of convulsions, but voluntary, and accompanied by every expression of joy and exhilaration. This may continue for hours, the animal then becoming gradually quiet, and passing finally into his normal condition. If instead of a moderate dose a toxic one has been given, there is first a period in which the animal is very restless but seems full of terror and anxiety; the least sound frightens him, causing him to tremble and to drop his tail between his legs. He does not appear at this time to know his master. Rhythmical movements of almost all portions of the body accompany this state. Fifteen or twenty minutes later the mental condition alters, and the dog becomes apparently full of joyous excitement. He barks loudly, runs from one person to another, licking them, and giving all the characteristic signs of joy. After a few moments this condition gives way to one of increasing feebleness; the dog gradually be-

comes unable to move, rhythmical movements, cramps, and convulsive symptoms appear; the pendulum-like swinging of the head gets very violent, and at last narcosis, with epileptiform convulsions, develops. It is evident that many of these symptoms are psychical.

Nervous System.—Cocaine acts with great power upon the cerebral cortex. The peculiar sense of calm which follows moderate doses of the drug is evidently the result of an influence which after large doses causes an exalted delirium.

The stimulating influence of cocaine upon the cerebrum is further shown in the results reached by Mosso,—namely, that the reaction time of elementary perceptions is lessened, although the drug produces no noteworthy difference in the capabilities of nerves of conducting impulses.

B. von Anrep believes that the drug has a very distinct and peculiar influence upon the *semicircular canals*, thereby causing the peculiar pendulum-like motions of the head, the lack of coördination, and the rolling convulsions especially seen in doves.

Spinal Cord.—According to the researches of Von Anrep, the convulsive movements are of cerebral origin, and are arrested by section of the spinal cord; but the experiments of L. I. Tumass[10] indicate that they do not arise in the psycho-motor centres of the brain-cortex, since he found not only that the local application of cocaine lessens the irritability of these centres, but also that during the convulsive stage of cocaine-poisoning the centres are less sensitive than normal. Danini, moreover, appears to have found that section of the cord does not prevent convulsions in the hind feet, and the experiments of Mosso show that when the upper cord is cut in the dog and the animal cocainized, the irritation of the nerve-trunk or of the surface will produce in a little while general muscular rigidity. Both Mosso and Von Anrep are in accord with other observers in stating that reflex activity is at first increased by cocaine, and the evidence seems to show that while the convulsive movements of the poisoned animal originate chiefly in the brain, yet there is a primary stage of excited reflex activity, the result of a direct action upon the spinal cord. The motor paralysis and the loss of reflex activity which finally occur in cocaine-poisoning are probably in part the result of an influence upon the nerves; but that they are chiefly due to a direct sedative action upon the spinal cord seems to follow from the experiments of Mosso, who found that when he so bound the hind legs of the frog as to prevent the access of cocaine to the nerves, there was a rapid loss of reflex activity, and indeed a complete paralysis, at a time when both the motor and the sensory nerves were still intact.

An observation made at a certain stage of the poisoning by Dr. Ott —viz., that irritation of the posterior column of the spinal cord produced no effect, while a prick of the anterior column was followed by the usual result—indicates that there is the same difference in action upon the sensory and motor tracts as upon the corresponding nerve-trunks; but Mosso's experiments upon tritons led him to conclude that the power of

conducting impulses efferently, or *from* the centre, is first lost in the spinal cord poisoned with cocaine.

Nerves.—Almost all observers agree that the *sensory nerves* after sufficient doses are finally paralyzed in cocaine-poisoning; but Mosso[11] believes that the respiratory centre is more susceptible to the action of cocaine than are the sensory nerves, and certainly doses of the alkaloid not dangerous to life have no perceptible general effect upon the sensory nerves. The experiments of Nikolsky, of B. von Anrep, of Ott, and of Laffont seem to prove that the sensory paralysis is preceded by increased functional activity, which is in accord with the observation of Mosso, that in doses of 0.05 to 0.1 gramme cocaine increases in man the sensibility of the skin.

According to Danini, the *motor nerves* in the frog remain irritable until after death; but, according to Nikolsky, their functional activity is first increased and afterwards destroyed. Ott also asserts that cocaine depresses the motor nerves. Moreno y Maiz found that when he tied the iliac artery of a frog on one side and administered cocaine anteriorly, there came a time when irritation of the poisoned limb caused no movement, while irritation of the protected extremity provoked very distinct general reflexes; at the same time there was diminished motility in the non-protected limb as compared with the protected one: facts which, of course, indicate that the drug finally depresses both motor and sensory fibres, but that its action upon the motor is subordinate to that upon the sensory nerves. Ott also noticed that there is a time in the poisoning when irritation of the central end of a cut sciatic nerve produces no response, while irritation of its peripheral end causes muscular action, and thereby confirms the view that the drug affects the sensory earlier and more powerfully than the motor nerves. H. Alms found[12] that a five per cent. solution of cocaine in contact with the isolated ischiatic plexus of the frog caused absolute anæsthesia of the leg and apparent loss of motor power, the leg lying motionless and trailing behind. Nevertheless, strong irritation upon the front leg of the frog caused immediate movements which were shared by the cocainized hind leg, showing that the motor filaments were not paralyzed. The experiments of Alms indicate that the extreme peripheral filaments of the nerve are first affected, since at a certain period most severe irritation of the skin produced no pain in the poisoned rabbit, although the injection of irritating materials evidently caused violent pain.

The discovery of Mosso, that the local application of cocaine suspends functional activity in motor nerves, has been confirmed by L. Popielski,[13] and it must be considered as demonstrated that cocaine is a *paralyzant to both motor and sensory nerves, although it acts much more powerfully upon the sensory nerves.*

Circulation.—The action of cocaine upon the circulation is in some details so complex that in spite of much work it is not yet fully understood, but in the main our knowledge concerning it is clear. The concordant

experimental results obtained by Ott, by Von Anrep, by Vulpian, by Laborde, by Nikolsky, by Danini, and by Reichert[14] show that the moderate dose of cocaine produces an increase in the arterial pressure.

It is true that some of these experimenters employed only non-curarized animals, but others practised curarization and artificial respiration, so that it must be acknowledged that whilst disturbance of the respiratory and muscular system, by the alkaloid may secondarily increase the blood-pressure, yet it has the power of directly increasing the arterial pressure. The fact that various experimenters have failed to obtain the increase of pressure just spoken of is in some cases to be explained by their having used too large doses, all investigators agreeing that the too large dose of cocaine finally decreases pressure; in other cases, when small doses of cocaine were employed (Berthold[15]), it is probable that so much curare had been given that the drugged heart and blood-vessels were unable to respond to a new poison: certainly the evidence is overwhelming that cocaine directly increases blood-pressure.

The experiments of Danini, of Berthold, and of Reichert are concordant in showing that after section of the spinal cord alone, or of the spinal cord and the vagi, cocaine does not distinctly increase the arterial pressure,—proof that the chief cause of the rise of the arterial pressure under the influence of cocaine is centric vaso-motor spasm.

Concerning the action of cocaine upon the heart itself there is such conflict of testimony as to require further experimentation before positive conclusions can be reached, but the drift of the present evidence is to show that the small dose of cocaine moderately stimulates the heart, and that the large toxic dose finally depresses it.

As showing the stimulant action of the small dose of cocaine, Mosso and H. G. Beyer,[16] as the result of their experimental studies, made in the one case on the cut-out frog's heart, in the other upon the isolated heart of the terrapin, found that the minute dose of the alkaloid increased the whole amount of force put out by the heart, as well as the power of the individual systolic contraction; whilst Pachon and Moulinier,[17] in experiments with cocaine on the heart of the frog *in situ*, find that after a moderate dose of cocaine there is a hypertonicity of the heart due to a direct action upon the muscular fibres. Observers affirm that the heart of the mammal is arrested by the toxic dose in diastole, which is in accord with the statements of Von Anrep and Nikolsky concerning the heart of the frog and of H. G. Beyer concerning that of the terrapin, diastolic arrest being affirmed by all these investigators. Pachon and Moulinier declare that the ventricles are arrested in systole, the auricles in diastole. According to these investigators, the arythmia of advanced cocaine-poisoning is really a rhythm which differs from the normal in that the contractions occur in regular groups; later there is a dissociation of the auricular and ventricular rhythms.

The fact that section of the spinal cord—that is, separation of the general capillaries of the body from the vaso-motor centres—largely or altogether prevents the rise of arterial pressure produced by cocaine indicates that the alkaloid has little or no direct influence upon the vessels themselves, but the matter is not as clear as appears at first sight.

The evidence as to the facts is contradictory. Mosso found that when he experimented with artificial circulation upon extirpated kidneys small doses of cocaine

had no sensible effect upon the blood-vessels; and Durdufi states that marked narrowing of the vessels of the rabbit's ear can be seen when cocaine is injected, but is prevented by previous section of the sympathetic. Contrariwise, H. G. Beyer found in experiments upon the terrapin that both large and small doses of cocaine produce contraction of the blood-vessels by a direct influence; and Laffont experimentally reached the conclusion that one of the chief actions of cocaine is to contract the blood-vessels by affecting the nerve-endings in their walls. The results of the plethysmographic studies of Mosso—namely, that in man therapeutic doses of cocaine cause contraction of the blood-vessels—have no bearing upon the matter in hand, since such contraction might or might not be of centric origin. It should also be stated that in some of Reichert's experiments there was a slight rise in the arterial pressure produced by cocaine after section of the cord.

The well-known constringing of blood-vessels by the local application of cocaine can hardly be explained except by attributing to the alkaloid the power of acting upon the blood-vessel walls. It should be noted that in such cases the cocaine is brought in enormous quantities and great concentration into contact with the blood-vessels; and in view of the contradiction in the experimental evidence, the most probable conclusion is that cocaine has direct relations with the muscle-fibres in the arteriole walls, but that it acts so feebly upon them in comparison with its influence upon nerve-centres that even in general poisoning with the alkaloid the influence upon the blood-vessel walls is overshadowed by the much greater powers of the drug.

The results of the studies made by various investigators with the direct application of cocaine to the heart lead to the conclusion that whilst small doses of the alkaloid feebly stimulate the viscus, toxic doses act as a depressant and finally as a paralyzant; that cardiac depression is one of the causes of low arterial pressure in advanced cocaine-poisoning is further evidenced by the rapid and immediate fall in the pressure which occurs when cocaine is injected into a dog whose spinal cord has been cut and vaso-motor system paralyzed.* The opinion of Reichert, that widening of the blood-paths by vaso-motor paralysis is the most important factor in the causation of lowered blood-pressure in advanced cocaine-poisoning, seems to be so far correct that the probabilities are that such widening of the blood-paths occurs.

The testimony as to the action of the alkaloid upon the pulse-rate and upon the inhibitory nerves of the heart is so various that no positive conclusions are warranted without further study.

Von Anrep states that the pulse-rate is usually increased, but that this increase is not marked in rabbits, while in Ott's experiments upon dogs the pulse usually becomes slower. Von Anrep also states that the vagi are paralyzed by large doses of cocaine, while Ott, Nikolsky, Laffont, and Durdufi[18] declare that it does not affect the vagi, and Berthold states that previous section of the vagi has no effect upon the course of the symptoms caused by cocaine.

Reichert found in an elaborate series of studies that by small doses of cocaine the pulse-rate is at first decreased, then increased, and finally decreased. In regard to the causes of the alterations of the pulse he came to the following conclusions:

* See experiments of I. Ott, *Toxicological Studies*, 1874, 30.

"Very small doses of cocaine decrease the rate by stimulating the cardio-inhibitory centres; small to moderate doses increase the rate by depressing these centres, and in some cases by depressing also the cardio-inhibitory ganglion; large doses cause a transient decrease, followed by a rise or a permanent decrease, the decrease being due to a depression of the accelerator or motor ganglion in the heart, and the increase to the factors before mentioned. The cardio-inhibitory centres are invariably affected, being primarily stimulated and secondarily depressed."

Muscles.—Although there is some contradiction of evidence, yet our knowledge of the effect of cocaine upon the striated muscles is sufficient for positive conclusions.

Alms, Nikolsky, and B. von Anrep state that the striated muscles are not affected by the alkaloid, while Ott affirms that it acts upon them like veratrine, and is confirmed in this by Buchheim and Eisenmenger.[19] The tracings given by Ott would appear to prove that the muscular contraction is prolonged by cocaine, and can hardly be accounted for by a condition which M. J. Rossbach and B. von Anrep allege to be produced,—viz., a peculiar sensibility of the muscle similar to that produced by curare, and, like it, caused by a lessening of muscle-tonus by paralysis of the peripheral nerve-endings.

The results obtained by Ott find such confirmation in the experiments of Berthold upon the effects of the local application of cocaine upon the frog's muscle, and in those of Mosso, who found that in the frog, the dog, and the man the excitability of the muscles is increased by small doses, and paralyzed by large doses of cocaine, that it must be considered established that cocaine is a *muscle poison, stimulating and afterwards depressing the functional activity.* This influence of the alkaloid is, however, probably too slight, as compared with its effects upon other portions of the organism, to be very apparent in general poisoning. Nevertheless, in the ergographic experiments of Benedicenti[20] cocaine both heightened muscular energy and increased resistance to fatigue,* whilst Mosso found that in man, when the muscles were exhausted by work and fasting, the exhibition of cocaine in the dose of a grain and a half more than doubled the response to stimuli. These experiments throw a peculiar light upon the assertions of travellers, that cocaine in the South American Indians enormously increases the power of withstanding fatigue. The present difficulty in the way of the full acceptance of the natural deductions from them is the fact that in America and in Europe cocaine has *appeared* to fail as a stimulant during fatiguing labors.

Temperature.—The rise of rectal temperature in cocaine-poisoning sometimes amounts to as much as 8° F. It is certainly not due to the convulsions, as it usually occurs before the motor disturbance.† In fatal

* Sobieranski believes, however, that the effect of cocaine is through the nerve-centres (see *Gazetta Lekarska*, 1896, No. 4).

† P. Langlois and Charles Richet have found that the temperature of the cocainized animal has a great effect in determining the amount of cocaine necessary to produce convulsions. The higher the temperature the smaller the dose necessary, and when the animal was kept at a temperature of 39° C., only tonic convulsions were produced.

cases it is followed by a fall, so that before death the temperature may become subnormal. In the calorimetrical experiments of Reichert, the rise of temperature was found to be due to a great increase in the heat production, but at present it is impossible to say why or how this rise of heat production is produced. The assertion of Mosso, that the rise of temperature occurs after section of the spinal cord, does not seem to be proved (see Reichert).

Urinary Secretion.—Such varying results have been recorded by clinicians as to the effect of cocaine upon the amount of urinary secretion that its action is probably not constant. According to Bignon,[21] the single large dose may produce an anuria so prolonged as to bring on uræmic symptoms. There is some reason for believing that cocaine reduces the nitrogenous elimination, but the experiments upon the subject are hardly sufficient to warrant the positive conclusion that the alkaloid checks protoplasmic waste.

I. Ott and Atherton P. Mason[22] have found that when cocaine is taken habitually it not only lessens the urinary secretion but also markedly decreases the elimination of urea, whilst in three experiments Richard Fleischer determined that the alkaloid markedly reduces nitrogenous elimination. Mason experimented with very large therapeutic doses of cocaine taken during prolonged exercise, and states that his results were contrary to those previously reached by Gazeau.

In Ott's experiments the urine, under the influence of cocaine, became full of calcium oxalates. Sugar and albumin have been frequently noted in the urine of poisoned animals, but Von Anrep affirms that their presence is due to the prolonged asphyxia induced by the drug.

Eye.—When a watery solution of cocaine is dropped into the eye there occurs a slight contraction of the pupil, followed within a few minutes by dilatation. The first contraction is probably reflex and due to the irritation of the conjunctiva. The maximum dilatation for a four per cent. solution is usually reached about the end of the first hour; an hour later it has sensibly begun to decline, and in from twelve to twenty-four hours the pupil returns to normal. The dilated pupil is to some extent responsive to light and to accommodation, the mydriasis can be rapidly overcome by eserine, and, according to Limbourg,[23] increased by atropinization.

For reasons which may be found given in detail in the tenth edition of this treatise, G. N. Durdufi[18] believes that the dilatation of the pupil produced by cocaine is of centric origin. This, however, is manifestly incorrect; by the local application of cocaine it is possible to dilate one pupil without affecting the other pupil. Further, the experiments of Nikolsky, Holtzke, Limbourg, as well as of Schöler and Pflüger (quoted by Limbourg), show that cocaine applied to the eye immediately after section of the sympathetic does dilate the pupil, although later, when sufficient time has elapsed for degeneration of the sympathetic fibres to occur, the alkaloid is powerless. Limbourg has made the curious obser-

vation that electrical irritation of the cornea may restore to such an eye the power of responding to cocaine. This change of sensibility may, perchance, be due to a stimulation of the nerve-filaments in the eye by the electricity.

It is certain that the ocular phenomena produced by cocaine are not of centric origin,* and although the matter has not been completely worked out, it seems probable that cocaine dilates the pupil by stimulating the peripheral sympathetic nerve.

Respiration.—Small doses of cocaine increase distinctly the rapidity of the respiration, and in some cases also the depth (Von Anrep, Mosso, Danini, Ott, and Nikolsky). After toxic doses the respirations become at first rapid and more shallow, then irregular with interruptions, after each of which the respiratory movements begin deep and slow, but become more rapid and shallow until the next stand-still. As Mosso found that after section of the vagi cocaine causes an enormous increase of the rapidity of the breathing and at the same time so modifies the rhythm that expiration is no longer quicker than inspiration, it must be considered that the drug acts directly upon the respiratory nerve-centres as a respiratory stimulant. The first stimulant effect of cocaine upon the respiratory centres appears to be followed after fatal doses by a paralyzing influence which leads to death from asphyxia.

Intestines.—According to Von Anrep, the intestinal peristalsis is markedly increased by moderate doses. After large doses this increase is followed by great sluggishness deepening into paralysis. Tarchanoff states that coca increases the mucous secretions, but Von Anrep affirms that it decreases them.†

SUMMARY.—Cocaine is a cerebral stimulant, producing peculiar mental excitement, ending after large toxic doses in narcosis, with epileptiform convulsions, which are probably of cerebral origin. In the poisoning there is at first increased reflex activity, followed by paralysis of voluntary motion and of reflex activity, which are chiefly due to a direct action upon the spinal cord, the sensory side of the cord being probably more sensitive to the drug than the motor side. Toxic doses depress and finally paralyze the sensory nerves, and in a much less degree the motor nerves. Our present physiological knowledge establishes the fact that cocaine in moderate dose is a mild stimulant, in overdose a depressant, to the circulation, the primary rise being chiefly due to narrowing of the blood-paths by stimulation of the vaso-motor centres. Upon the heart itself the moderate dose of the alkaloid acts pri-

* Dr. Jackson affirms that cocaine causes a peculiar irregularity of the corneal surface which is not due to any loss of epithelium, although it may proceed so far as to cause a notable haziness. Würdinger produced distinct corneal opacity in the rabbit by repeated instillations of a five per cent. solution. It seems, however, probable that this opacity was the result of corneal inflammation due to the inability of the anæsthetized eye thoroughly to protect itself; nevertheless, some oculists affirm that cocaine distinctly predisposes the eye to excessive inflammation upon irritation or operative procedures.

† M. E. Gley states (*Compt.-Rend. Soc. Biol.*, iii. 560) that when cocaine is injected into the portal vein it produces comparatively little effect, and he believes that it is destroyed in the liver. This is criticised by Chouppe (*Ibid.*).

marily as a stimulant, increasing to a slight extent the amount of force put forth by the heart. There is also reason for believing that cocaine exerts a direct influence upon the coats of the blood-vessels, which is, however, so feeble as not to be of practical importance except when the cocaine is applied locally. The fall of blood-pressure produced by the toxic dose of cocaine appears to be due to a direct depression of the heart itself, aided by a widening out of the blood-paths, probably through paralysis of the vaso-motor centres. Upon striated muscles cocaine appears to have a peculiar though very feeble action, which is not manifested during poisoning by it. It has been asserted that cocaine acts as a powerful diuretic, but the drift of present evidence is to show that it has no definite influence upon the amount of urine secreted: the evidence available indicates that it decreases elimination of urea. Upon the eye cocaine acts as an energetic mydriatic. It is a powerful stimulant to the respiratory centres, increasing the rapidity and fulness of the respirations, but if the dose be sufficiently large it after a time causes the respirations to become very shallow, and finally paralyzes the respiratory centres. Moderate doses are said to increase, large doses to paralyze, peristalsis.

THERAPEUTICS.—Cocaine acts with certainty as a local anæsthetic whenever it can reach the nerve-filaments in sufficient concentration. The skin will not allow it to pass, while the conjunctival and nasal mucous membranes are very permeable, and those of the larynx, throat, and vagina are penetrated with more and more difficulty, in the order of their naming. Even in disease of the eye, when a deep operation is to be performed, the solution of the anæsthetic must be reapplied at various stages of the operation. To the nasal surgeon the alkaloid appears to be invaluable, while the gynæcologist finds it less serviceable, but even he is, by its careful use, able to perform many operations without pain. In painful *ulcers*, *fissures of the anus*, etc., its application will afford temporary relief.

There is truth in the original assertion of F. H. Bosworth, that cocaine possesses distinct hæmostatic powers, so that it may be useful in arresting *nasal hemorrhage*. It also is of some service in overcoming acute congestions and inflammations of mucous membranes to which it can be applied directly, and especially is it valuable when with the inflammatory condition there is an excessive local nervous irritability of the part. In acute *coryza* a ten per cent. solution applied to the nostrils will sometimes afford permanent relief, but a combination of a four per cent. solution with bismuth (three drachms to the ounce of mucilage) is more generally useful. It should be applied by means of a dropper every three or four hours. In *hay fever*, in the peculiar irritated sore throat of *advanced phthisis*, in chronic *laryngitis*, in *inflamed hemorrhoids*, even in open ulcerated *cancers* and other painful affections, cocaine as a palliative is invaluable. In *boils* and *carbuncles* it must be injected directly into the part in order to afford relief.

Cocaine is largely used by oculists in the treatment of *conjunctivitis* and in various operative procedures. The assertion made by Keyser in

1894, that the ischæmia which it at first produces is followed by great relaxation of the vessels and secondary inflammation, though having some basis in truth, is not fully confirmed by later general experience. The tendency to after-congestion is very rarely sufficient to be of importance. Many ophthalmologists refuse to use the alkaloid in *ulceration of the cornea*, believing that it has a special deleterious influence on the corneal epithelium, and is capable even of causing shedding of the superficial layer.

The production of local anæsthesia, as suggested by Hall and Halsted,[24] by injecting a strong solution of cocaine into the supplying nerve-trunk, though theoretically possible, has so many practical disadvantages that it has not come into vogue.

A. Bier,[25] and subsequently Seldowitsch [26] and Tuffier,[27] have practised the injection of cocaine into the spinal canal as a means of producing extensive anæsthesia for surgical purposes. A large number of resections, amputations, and other major operations upon the lower extremities have been performed in this way, with asserted complete success so far as the absence of pain is concerned. A hollow needle is introduced into the vertebral canal, as in the operation of lumbar puncture, and from one to two centigrammes (one-sixth to one-third grain) of cocaine dissolved in one to two cubic centimetres of sterilized artificial serum are injected. The loss of sensation in the lower extremities is said to be complete in ten minutes and to last for about one hour. Some surgeons fail to note any evidence of cocainism. Seldowitsch, however, records chill, slight rise of temperature, and increased frequency of the pulse in all cases; headache, vomiting, and excitement in a minority of them. It seems to us that the results are largely due to pressure upon the spinal cord and nerve-roots by the injected serum, and further experience is certainly necessary before the safety of the plan can be considered assured, the chief danger being the possible starting of spinal inflammation.

For local use a four to ten per cent. solution may be employed, and when the part is not readily permeable, as in the vagina, it should be thoroughly reapplied once or twice at intervals of five minutes. Many minor surgical operations can be performed without pain by injecting cocaine hypodermically and restraining the circulation by pressure. Thus, if a tight band be placed around the proximal end of the finger, and cocaine injected, a *felon* may be opened freely without suffering. In a similar way a tumor may be incised from a lip, or a hare-lip operation performed, if pressure be made around the part by a wire clip. Even in the trunk a superficial tumor may often be removed without suffering after a concentric series of minute injections of a solution of cocaine around its base. In the so-called *infiltration-anæsthesia*, as devised by Schleich, the loss of sensibility is largely due to the stretching of the tissues by the injected solution, with the consequent interference by pressure with the circulation and with the peripheral nerve-filaments them-

selves. The skin having been frozen by means of the ethyl spray, the point of a large hypodermic syringe is thrust into its papillary layer and a small mass of the fluid is injected, not under, but into, the skin. The needle of the syringe is then pressed in a little deeper and a new injection made, the process being continued until a sufficient depth is reached. This method has been applied not only in minor but also in major surgery. During a large operation the injection has to be repeated from time to time as the knife of the surgeon cuts more and more deeply into the tissues.

Three solutions were used by Schleich. No. 1, of medium strength, may be made by dissolving at the time of using a powder composed of one and a half grains of cocaine hydrochlorate, one-third of a grain of morphine hydrochlorate, and three grains of common salt in twenty-seven drachms of sterilized water. No. 2, the weakest solution, contains only one-tenth the percentage of cocaine in No. 1 ; whilst No. 3, the strongest solution, contains double the percentage. No. 3 is used only when there is an active inflammatory lesion of moderate extent, as in case of a *furuncle*. In many cases it is essential that not only the part to be opened but the tissues beneath it be infiltrated. Thus, a furuncle or abscess may be completely encompassed with a zone of artificial œdema.

FIG. 6.

Showing mode of injecting the fluid under an abscess in successive whorls. (Schleich.)

FIG. 7.

Showing the syringe-point in the papillary layer of the skin.

Internal Use.—As an internal medicament cocaine is useful as a respiratory stimulant and as a tonic especially to the circulation. It is largely used in the same class of cases in which strychnine is found to be available. Less powerful in its influence than is strychnine, it is especially useful as an aid to that alkaloid. (See *Respiratory Stimulants.*) Its stimulant influence upon the cerebrum naturally led to the expectation

that it would be of value in cases of depression of spirits and even of true *melancholia*. The results of our own experience, after thorough trial, however, are in accord with the generally expressed opinions of alienists, that it has no remedial value in any cases of mental aberration. Sometimes it appears to produce at first a temporary relief, but this does not continue ; and if the remedy be pushed, anorexia, restlessness, or other disagreeable symptoms usually demand its withdrawal. In *neurasthenia* and *hysteria* it is valuable only as a stimulant and stomachic, acting better in the form of the fluid extract than cocaine itself ; and in all these cases there is especially the danger of the formation of the cocaine habit. Large doses of the fluid extract are sometimes of service.

In the form of large doses of the fluid extract, coca has appeared to us to be of service during the breaking off of the *opium habit*, exerting some stimulant influence upon the nervous system, and restraining the tendency to diarrhœa and loss of appetite. Some European clinicians have found cocaine of service in the treatment of *serous diarrhœas*. It is undoubtedly of value for the relief of *excessive vomiting*, especially when due to gastric irritation. Thomas D. Dunn[28] states that hypodermic injections of one grain control the pain of *migraine*. Aschenbraidt[29] asserted that, in doses of 0.15 grain, cocaine was a valuable stimulant during forced marches ; but in a series of careful trials with it by the medical rowing crew of the University, it appeared to have no value, and the general experience seems to conform with this result.

ADMINISTRATION.—The official salt of cocaine (COCAINÆ HYDROCHLORAS, U. S.) may be given in doses of one-sixth to one-half a grain (0.01–0.03 Gm.) ; the cruder preparations of the drug are at present rarely used. The dose of the official fluid extract (EXTRACTUM COCÆ FLUIDUM, U. S.) is one-half to two fluidrachms (1.9–7.5 C.c.).

TOXICOLOGY.—The number of cases of poisoning by cocaine is very great, and although large doses have been recovered from, excessively violent symptoms have followed the use of smaller amounts. It is remarkable, also, that in many of these cases the drug has been employed for a local effect.

The fatal cases, to the details of which we have had access, are those reported by Kolomnin, twenty-four grains into the rectum for local anæsthesia ; F. M. Thomas, four per cent. solution used locally for toothache, in unknown quantity ; Knabe, four per cent. solution, twelve drops given hypodermically to a girl of eleven years, death in forty seconds (for details, see J. B. Mattison[30]) ; J. H. C. Simes,[31] one drachm of twenty per cent. solution injected into the urethra, followed immediately by violent convulsions, ending in death in twenty minutes, autopsy proved that urethra was not ruptured. A fatal case is said to have been reported in *Odontologie*, 1890, x. Half an ounce of a two per cent. solution of cocaine injected into hydrocele and allowed to stay about a minute is said to have caused death (Paul Berger[32]). O. H. Garland,[33] death said to have been produced by the application of twenty drops of a five per cent. solution to the gum. E. Pfister,[34] death caused by an unknown quantity of a twenty per cent. cocaine solution injected into the urethra.

On the other hand, large amounts of the drug have been recovered from.

Von Ploss[35] reports twenty-two grains taken by an apothecary, by the stomach, with spontaneous recovery, although the urine was suppressed for twenty-four hours. In another case ten grains taken hypodermically in the course of five hours produced complete unconsciousness, excessive failure of circulation, slow respiration, recovery under treatment (J. S. Spear[36]); E. Caudwell[37] reports recovery after the hypodermic injection of five grains, which produced convulsions with asphyxia. A case reported by W. Finlay[38] is interesting, because six grains given hypodermically to a pregnant woman lowered the pulse to 38 and the breathing to 5, but did not cause a miscarriage.

Some of the most remarkable cases of poisoning by small quantities are those reported by T. H. Burchard, ten drops of a four per cent. solution injected hypodermically caused unconsciousness and apparent death in four minutes; Myerhausen, eight drops of a two per cent. solution upon the conjunctiva produced in a girl of twelve years violent symptoms; Kennicott, a case of violent symptoms produced by cocaine in hay fever; George T. Stevens, one in which four minims of a three and a half per cent. solution, given to a strong man, produced violent convulsions, followed by mania; Grosholz, three drops of a four per cent. solution in the eye; Frost, one drop of a one per cent. solution in the eye produced in a child of fourteen marked poisoning; Ramsden Wood[39] reports violent poisoning with four minims of a twenty per cent. solution. A number of cases are on record in which very severe symptoms have been produced by one grain given hypodermically (see Mattison, Addinsell,[40] and Pitts[41]); and it is plain that, although this dose has been used to a considerable extent, its employment is unjustifiable. The occasional effects of the local application of cocaine are very remarkable.*

It is not safe to put upon mucous membranes amounts which if given hypodermically would be dangerous; so that not more than three-quarters of a grain should be used locally.

The treatment of cocaine-poisoning must be largely symptomatic. When there is great cerebral and motor excitement, we have found chloroform to act very happily. Partial anæsthesia may be maintained for some moments. If the symptoms do not yield to such medication, chloral may be cautiously exhibited. When the toxic manifestations are syncopal, hypodermic injections of digitalis may be given, whilst alcohol and ammonia are exhibited by the mouth; if circumstances favor, intravenous injections of ammonia might be justifiable. In some cases life has been apparently saved by artificial respiration. Intravenous injection of salt solution has been recommended.†

Cases of *cocainismus* or chronic cocaine habit are not rare, but in the great majority of instances the victim is addicted to the use of more than one narcotic. Usually the cocaine has been taken as a substitute for, or

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* In addition to cases mentioned, see *Brit. Med. Journ.*, Nov. 1885; *Deutsch. Med. Wochensch.*, No. 46, 1886; *New York Med. Rec.*, 1886, ii.; *La Pratique Méd.*, Jan. 1891; *S. J.*, cclvii. 201.

† *Systemic Lavage for Poisons.*—Intravenous injection of normal saline solution as a treatment for acute poisoning has been experimented upon by Carlo Bozza (*Canadian Pract.*, 1898, xxiii.), who believes that it leads to rapid elimination and slow absorption, owing to fulness of the blood-vessels. He determined that the minimum fatal dose of cocaine given to dogs hypodermically is 0.025 gramme per kilo; rising to 0.03 if hypodermoclysis is employed, and to 0.035 with lavage of the organism.

aid to, morphine : in a number of cases the habit has been formed by the local use of the drug for *hay fever*. The symptoms are in no way characteristic ; dreaminess, apparent inability to attend to the ordinary duties of life, loss of reliability, promptness, and punctuality, varying mental aberration suggesting, but different from, that of paranoia, occurring in any case, should arouse suspicion. The paranoiac, unless greatly depressed, is usually egotistical, self-reliant, conceited ; the victim of cocainism, in matters not connected with his habit, is usually even less self-assertive and more easily led than the normal individual. Magnam [42] affirms that a peculiar hallucination as to the existence of foreign bodies under the skin is characteristic.

The will and the desire to reform are as weak as in the opium habit, and the greatest difficulty is usually to get the victim earnestly to desire reformation. The abrupt withdrawal of the narcotic is probably always safe ; thus, in a case in which fifteen grains were taken hypodermically daily, the immediate cessation of exhibition was followed by no greater disturbance than diarrhœa, dyspepsia, and nervous depression, which subsided in the course of two or three days. (For cases, see Grundlach [43] and Mattison.[30])

EUCAINE.

Under the name of eucaine two allied chemical substances have been put upon the market as local anæsthetics, each of them depending, according to Vinci,[1] for its anæsthetic properties upon the presence of the benzoyl molecule in its constitution. These substances have been distinguished in commerce by the names of Alpha-Eucaine and Beta-Eucaine. Alpha-Eucaine is chemically n-methyl-benzoyltetramethyl-y-oxypiperidincarboxylicmethylester ; Beta-Eucaine is benzoylvinyldiacetonalkamine.

Alpha-Eucaine is the substance usually sold in the markets under the name of Eucaine. It is a white, neutral, crystalline powder, soluble in ten parts of cold water ; originally proposed for use in medicine by G. Vinci.[2] *

The local anæsthetic influence of eucaine is exerted with great promptness, so that a two to five per cent. solution will completely anæsthetize the cornea in from one to three minutes without dilatation of the pupil or abolition of the pupillary reflexes. The anæsthesia continues from twenty to thirty minutes. There is no ischæmia due to contraction of the blood-vessels as in cocaine anæsthesia, and no paralysis of accommodation.

In the experiments of Vinci and also of Ver Eecke,[3] eucaine produced in the lower animals marked excitement, with heightened reflexes and incoördination of movement, followed after sufficient doses by tonic and clonic convulsions, ending in dyspnœa and progressive paralysis ; or, if recovery occurred, in or rather through

* Beta-Eucaine is said to be free from irritating properties and less toxic than Alpha-Eucaine. According to Vinci, it paralyzes the peripheral motor nerves as well as the sensory, does not dilate the pupil, paralyzes the vaso-motor centres, and slows the heart even after the vagus has been paralyzed with atropine.

a convulsive condition to the normal. As in Vinci's experiments galvanization of the sciatic nerves produced movements in the tributary muscles, it would appear that eucaine acts upon the spinal cord itself. Ver Eecke states that it is a direct muscle paralyzant, complete loss of muscular power never being reached in poisoning by it because the heart-muscle is more susceptible to the influence of the poison than are the voluntary muscles, so that cardiac diastolic arrest occurs before complete general paralysis.

According to Ver Eecke, in the mammal eucaine causes, first, fall, then rise of the arterial pressure, followed by a fall with marked oscillation, if the dose be large enough, the immediate causes of these changes being unknown. The same investigator states that eucaine first stimulates and finally paralyzes the respiratory centres. The statement of Ver Eecke, that the drug causes increased destruction of nitrogenous tissues, is scarcely borne out by the tabulated reports of his experiments. Ver Eecke failed to find the poison in the urine after its administration, and believes that it undergoes destruction in the body.

The efficiency of eucaine as a local anæsthetic seems established, whilst its influence upon the general system is so slight that fifteen grains of it have been injected hypodermically (G. W. Spencer[4]) without the production of any marked symptoms. On the other hand, Fuller affirms that it produces a peculiar hardness of the tissues which interferes with the use of sutures, and Keen informs us that in the Jefferson College Clinic sloughing has followed its use in three cases. W. M. L. Coplin believes that the sloughing is a coagulation necrosis, because he has found that the application of a one per cent. solution of eucaine to the peritoneum induces a stasis which is not affected by the free use of normal salt solution, but is broken up by the application of even a dilute watery solution of the amyl nitrite.

There are very largely used for the purposes of dental anæsthesia in the United States certain proprietary solutions whose activity probably depends upon the presence of eucaine, and whose success is largely due to an infiltration anæsthesia produced by the very free hypodermic use of the liquid around the tooth to be withdrawn. As the result of this method we have seen severe sloughing of the mucous membranes of the mouth occurring in persons of excellent health. The local accidents produced by the injection of eucaine are exceedingly interesting in connection with the statement of Ver Eecke, that in chronic poisoning by eucaine there is a wide-spread fatty degeneration showing itself markedly in the heart-muscles.

TROPACOCAINE—BENZOYL-TROPEIN.

This alkaloid was isolated by Giesel from the narrow-leaved coca-plant of Java. It is obtained as an oily liquid, which solidifies in radiating crystals, and is soluble in chloroform, ether, or benzin. It has been physiologically studied by Arthur P. Chadbourne, who finds that locally it acts in a manner similar to cocaine, without, however, causing ischæmia or congestion of the mucous membrane with which it is brought in contact. It was found by Chadbourne to be only half as toxic as cocaine. In lower mammals it produces in sufficient dose loss of co-

ordination, followed by violent convulsions, disturbances of the respiration, coma, and death by centric asphyxia. The convulsions are of cerebral origin. Upon the circulation the drug seems to have only a comparatively feeble influence, causing, however, when in sufficient amount, a steady fall in the arterial pressure. The temperature usually begins to rise before the convulsion, and has been noted as high as 4° C. above the normal. When tropacocaine is put in the eye, anæsthesia is said to come on and disappear more quickly than with cocaine, sensation being suspended in less than half a minute after the application of a three per cent. solution : mydriasis is usually absent, never very pronounced.

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FAMILY V.—EXCITO-MOTORS.

In this class are included such drugs as increase the reflex activity of the spinal centres, and thereby give rise to disturbance of motility. The only representatives of the class used by the practitioner of medicine are those drugs which contain strychnine as their active principle.

NUX VOMICA—NUX VOMICA. U.S.

The seeds of Strychnos Nux-vomica, a middle-sized tree growing in the East Indies, whence the drug enters commerce. They are circular, nearly flat disks, a little less than an inch in diameter, covered with very short, satin-like, grayish hairs; internally they are tough and horny, and are possessed of an intensely bitter taste. They contain two alkaloids, —strychnine and brucine,—existing in combination with an acid, the so-called *igasuric* of Pelletier and Caventou, which, according to Husemann, is identical with malic acid.

The U. S. Pharmacopœia recognizes the extract (Extractum Nucis Vomicæ), of which the dose is one-fourth of a grain (0.016 Gm.), equivalent to about one-twenty-seventh of a grain of total alkaloids; the tincture (Tinctura Nucis Vomicæ), of which ten minims represent one-thirty-fifth of a grain of total alkaloids, dose from ten to fifteen minims (0.60–0.90 C.c.), fifteen to twenty-five drops; and the fluid extract (Extractum Nucis Vomicæ Fluidum), which is required to assay one and one-half grammes of total alkaloids in one hundred cubic centimetres; dose three minims (0.18 C.c.) containing about one-twenty-third of a grain of alkaloids. It is usually estimated that strychnine constitutes about forty per cent. of the alkaloids. Practically there is no qualitative difference between the medical action of strychnine and that of the cruder preparations of nux vomica, over which it usually should have the preference on account of definiteness of action.

STRYCHNINA. U.S.

As kept in the shops, strychnine is a grayish-white powder, but by slow crystallization from its alcoholic solution it may be obtained in octahedral or quadrilateral prisms. It is so bitter that it will impart a very intense bitter taste to twenty thousand times its weight of water. On account of its insolubility (one in about seven thousand parts of cold water) it is very rarely used in medicine, at least in the United States, the sulphate (Strychninæ Sulphas, U. S.) being universally

preferred, and being what is commonly meant in American writings when the word "strychnine" is used. Strychnine sulphate contains about seventy-five per cent. of strychnine. The ordinary dose is from one-fortieth to one-twentieth of a grain (0.0016–0.0032 Gm.).*

PHYSIOLOGICAL ACTION.—*Local Action.*—The local action of strychnine is that of a very feeble irritant; upon the mucous membrane of the stomach it acts like a simple bitter.

Absorption and Elimination.—Strychnine is absorbed rapidly, whether taken by the mouth or by hypodermic injection.

Several investigators have attempted to determine the comparative rate of absorption of strychnine in different portions of the alimentary canal by isolating these different portions by ligatures and then injecting strychnine into them. After tying of the pylorus, Bouley and Colin[1] found that the absorption of strychnine was rapid in the stomachs of dogs and cats, whilst Tappeiner determined that in cats it was taken up very slowly. In two series of experiments, S. J. Meltzer[2] found that, after tying the cardiac and pyloric ends of the stomach, large doses of strychnine would remain in the stomach of the rabbit without producing any physiological effect, whilst under similar circumstances in the dog the gastric absorption was extremely slow and uncertain. Meltzer further determined that absorption takes place in the œsophagus somewhat more rapidly than in the stomach, whilst the alkaloid was taken up with great and about equal avidity in the small intestines, colon, and rectum. Although the method of investigation is open to the objection that the operative procedure may seriously disturb the mucous membrane of the part, and consequently its absorbing power, it is probable that the results of Meltzer are substantially correct.

Strychnine has been detected by chemists in the blood, kidney, liver, heart, brain, spinal cord; indeed, practically in all portions of the system. The statement of R. W. Lovett,[3] that it accumulates in the spinal cord, has been disproved by Ipsen and by Lesser.[4] It may be in excess in the organs concerned with absorption and elimination, as in the stomach, liver,† and kidneys, but seems to be nowhere else present in the body of the poisoned animal or man out of proportion to the amount of blood going to the organ.

It is certain that strychnine escapes from the body to some extent unchanged, as it has been found in the urine by Peter von Rautenfeld,[5] by Wormley,[6] by Schauenstein, by Kratter,[7] and by Dixon Mann. Its elimination is prompt and rapid, as Ipsen asserts that it can be found in

* Thoinot and Brouardel (*La Presse Méd.*, 1898, i., Annex, 127) found that when strychnine is macerated with the spinal cord and brain, or with potato starch, the toxicity is so far lost that double the ordinary fatal dose of the alkaloid is required to kill guinea-pigs. When the nerve-tissue mixture was filtered, the filtrate was without toxic action. The strychnine could, however, be recovered from any of the mixtures, and when separated was found to be physiologically active. The loss of toxicity is therefore not due to its destruction. The authors believe that the loss of activity is due to the strychnine being so fixed as to interfere with its absorption. Talc and charcoal were found to have the same properties as nerve-tissue to a slight degree.

† Schiff and Lautenbach believe that they have proved that the alkaloid is destroyed, at least in part, in the liver; a conclusion which is strongly combated by Chouppe and Pinet (*Compt.-Rend. Soc. Biol.*, 1887, cv.), and is very doubtful.

the urine five minutes after its absorption, and others have detected it in the urine half an hour after its exhibition ; and in various poisoning cases, fatal within two hours, it has been found in the urine. Kratter and Mann believe that they have proved that the elimination is complete within forty-eight hours. According to P. C. Plugge,[8] a portion of the alkaloid is converted into *strychnic acid.*

General Action.—According to the experiments of Borzi,[9] strychnine paralyzes the sensory organs of *plants*, but increases the tension (motor function) of the plants : solutions as low as 1 in 10,000 acted distinctly upon vegetable protoplasm, and when the plant was apparently killed by strychnine, chloroform or paraldehyde would restore its functional activity.

Upon all animals strychnine probably acts similarly, but with great variations of power.

According to Leube,[10] it takes ten times as much strychnine to kill chickens as it does to kill other birds, weight for weight ; and among mammals the guinea-pig is very insensitive to it. It has also been asserted that on some monkeys it has but little influence (*Boston Med. and Surg. Journ.*, 1872). Very young animals are said to be quite insensitive to it.*

When taken in quantities just sufficient to produce sensible physiological effects, strychnine in man induces a feeling of restlessness, perhaps accompanied by tremblings in the limbs and some stiffness in the neck and jaws. When a somewhat larger amount has been given, there may be general muscular twitchings and startings, with stiffness and stricture of the throat and chest ; formications or other abnormal sensations under the skin may or may not be present. After poisonous doses the symptoms come on usually in from fifteen to twenty minutes, rarely after an hour, with great suddenness ; sometimes the convulsions are preceded by partial spasms of the muscles of the extremities, but more often the patient is suddenly thrown down by a general tetanic spasm. In this the body is bent backward and rests upon the heels and the head, in a condition of opisthotonos ; the legs are rigidly extended and the feet everted ; the arms bent and the hands clinched ; the eyes staring, wide open ; the corners of the mouth often drawn up so as to produce the *risus sardonicus.* The senses may be sharpened, but ringing in the ears and dimness of vision may be induced if the fits are severe. The face is at first pale, but, if the fit be sufficiently severe and protracted, it becomes livid from the interference with respiration. Consciousness is not affected, unless when asphyxia becomes so pronounced as to threaten death ; in such cases sometimes a period of insensibility precedes dissolution, but generally the intellect is clear to the moment of death. The muscles of the jaw are usually the last in the body to be

* See *Arch. f. Ges. Physiol.*, 1884, xxiv. 530; also Behrend Lau (*Elmshorn Inaug. Diss.*, 1886).

affected, but trismus finally comes on in severe cases. We have seen death occur in this first convulsion in animals ; but Tardieu states that he knows of no such instance in man (compare case of Demme[11]). After a time the paroxysm is at an end, the jaw drops, the muscles relax, and a period of calm comes on, to be succeeded by a second convulsion like the first. These convulsions are excited by the slightest touch, by a draught or breath of air, even by a loud sound ; but a firm grasp or hard rubbing of the muscles is frequently grateful. A slight rigidity is sometimes manifest between the paroxysms, but no marked stiffness. The spasms are generally, but not always, very painful. There are often erections of the penis, and the fæces and urine may be passed involuntarily. If the case terminates favorably, the convulsions gradually lessen in intensity, and fade away, leaving the patient exhausted, with a sore, tired feeling in the muscles. After death, post-mortem rigidity is developed very quickly. Autopsies have revealed nothing but the usual congestive lesions of death from asphyxia, and, at times, indications of spinal hyperæmia.

Cerebrum.—So far as our present knowledge goes, strychnine has little or no influence upon the cerebral cortical centres. The stimulation of the special senses sometimes seen in the beginning of strychnine-poisoning is probably, though not certainly, peripheral in its origin ; and consciousness is probably never directly affected by the drug.

Spinal Cord.—The spinal origin of the convulsions of strychnine has been demonstrated by a large number of experimenters. They occur after section of the spinal cord below the point of division. In Brown-Séquard's experiments, confirmed by Martin-Magron and Buisson, when the spinal cord was severed just below the origin of the nerve supplying the fore legs of the frog, and the lower section of the cord isolated by cutting its blood-vessels, strychnine produced convulsions in the anterior part of the body, whilst the posterior segment of the body was quiet and retained its normal reflexes, although the blood was carrying strychnine to every part of it except the spinal cord. It has been proved by Van Deen, by Valentin, and by A. J. Spence* that when strychnine is placed upon the cut upper surface of the brain or spinal cord so that it will diffuse itself within the spinal cord without being carried by the circulation, convulsions appear in those muscles whose nerves have their origin near the point of application, and spread from muscle to muscle as the poison creeps through the cord. The accuracy of the statement of Claude Bernard,[12] that when all the posterior nerve-roots are cut no convulsions occur, whereas, if a single afferent root remains, irritation of

* Some of the phenomena stated by Spence to have occurred are at present very difficult to explain. Thus, he noted that as the poison travelled down the cord there was a time when irritation of the fore feet caused only spasm in them ; later in the experiment, irritation of the front feet caused spasm of both the front and hind feet, although irritation of the latter did not produce other than normal reflex movements ; later still in the poisoning came a stage when irritation of the front legs was powerless to cause spasm in the hind legs, although irritation of the latter would now cause spasm in the former.

its nerve will cause general tetanic spasm, has been denied by Spitzka, but is probably correct. If so, it demonstrates that the reflex motor ganglionic cells are incapable of originating an impulse, and in strychnine-poisoning are simply in such a condition of over-excitability as renders them exceedingly sensitive to slight irritations and causes them to respond most energetically to the feeblest stimulus, the convulsion always being therefore a reflex phenomenon.

That the action of the alkaloid is upon the motor centres of the cord seems further to be demonstrated by the ingenious experiments of Van Deen,[13] who so divided all the tissues that the anterior portion of an eviscerated frog was connected with the posterior solely by the posterior columns of the cord. When one or two drops of a solution of strychnine were placed in the mouth of the prepared batrachian, tetanus, confined to the anterior segment of the body, was developed; and it was also found that while irritation of the posterior feet caused in them only ordinary reflex movements, in the front legs tetanic spasms were simultaneously induced.

Strychnine is evidently a powerful stimulant to the motor cells of the whole spinal tract up to the pons Varolii. In this stimulation, however, the cortical portion of the pyramidal or motor tract appears not to share, for Biernacki[14] has found that in the strychnized rabbit the psycho-motor centres in the brain are less susceptible to stimulation than in the normal animal. Biernacki's conclusion, that this loss of function in the psycho-motor centre is not due to any direct influence, is probably correct.

Motor Nerves.—After death from strychnine, the functions of the motor nerves are always found to be more or less impaired, so that galvanization of the nerve-trunk produces either very feeble contractions in the tributary muscles or none at all.*

That the exhaustion produced by the excessive number of violent impulses which travel along the motor nerves during the period of strychnic convulsions is a distinct factor in causing the loss of functional power in the nerve-trunk was proved in 1856 by Kölliker,[15] who found that when he cut the sciatic nerve in the frog and exhibited strychnine the divided nerve would respond to galvanic stimulation after all functional power had been lost in the nerve whose connection with the centres was intact. These experiments have been confirmed by Martin-Magron and Buisson, and must be accepted. Nevertheless, it has been demonstrated by Vul-

* See Matteucci (*Traité des Phénomènes électro-physiologiques*, Paris, 1844), Moreau (*Comptes-Rendus Soc. de Biol.*, 1855), M. Ambrosoli (*Gazette Médicale*, 1857, 525), Wittich (*Bericht d. Fortschritte d. Anat.*, 1857, 434), Kölliker (*Virchow's Archiv*, 1856, x. 239), and Vulpian (*Archives de Physiologie*, Nov. 1870, 125). The statement of W. H. Klapp, that he has found in thirty-seven experiments the motor nerve unimpaired in the frog after death from strychnine (*Journ. Ment. and Nerv. Dis.*, Oct. 1878), may depend upon the fact that in some species of frogs the nerves are extraordinarily refractory to the action of strychnine, or it may be that he employed such powerful stimuli that all apparent differences were lost. Sautesson found that strychnine acts twelve times more powerfully upon the nerves of *Rana esculenta* than upon those of *R. temporaria*.

pian, by E. Poulson,[16] by C. G. Sautesson,[17] and others, that strychnine has a direct paralyzing action upon the peripheral motor nerves. When the nerve has been divided, as in the experiments of Kölliker, it finally becomes paralyzed in strychnine-poisoning; and Vulpian has found that if the doses have been properly adjusted the motor nerve after a time will regain in the poisoned frog its activity before stimulation of the spinal cord has altogether passed off, so that the history of such an experiment is, first, tetanus,—then paralysis, due to the loss of power by the nerve-trunks,—and then again a tetanus which gradually subsides into the normal condition. Further, as pointed out by Richet, and as we have frequently seen, if an enormous dose of strychnine be injected into the jugular veins of the dog, death immediately results practically without convulsion, it being possible by artificial respiration to maintain the circulation for a considerable length of time. Under these circumstances the motor nerves will be found to have entirely lost their power of responding to galvanic or other stimulation, although they may still be able to transmit sufficient afferent impulses from the spinal cord to produce slight but distinct choreic muscular contractions.

Sensory Nerves.—The afferent or sensory nerves appear not to be affected by strychnine. Martin-Magron and Buisson having tied all the tissues of a hind leg of a frog except the nerve, and injected strychnine into the body of the batrachian, found that at a time when convulsions had ceased in all portions of the body except the leg to whose nerve the poison had not had access, slight irritation of the poisoned foot would induce tetanic spasms in the protected leg, thus showing that though the motor nerves to which the strychnine had had access were completely paralyzed, the afferent nerves were still functionally active.

Circulation.—The full dose of strychnine produces a rise of the arterial pressure which is enormously increased during the convulsion, after which there is a very pronounced fall in the arterial pressure.* The primary rise is not due to the convulsion, since it precedes the convulsion, and occurs in curarized animals. It is largely due to vaso-motor contraction, since Mayer,[18] Klapp,[19] and Reichert[20] have all found that after paralysis of the dominant vaso-motor centres by section of the cord, strychnine causes no rise at all,† or an exceedingly slight one, of the arterial pressure. The fall of the arterial pressure has been shown by Klapp and Reichert to be due, in part at least, to paralysis of the vaso-motor centres. By the intravenous use of very large doses of strychnine it is possible to produce immediate paralysis of those centres, with corresponding fall of the arterial pressure.

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* See also Richter (*Zeitschrift f. ration. Med.*, 1863, xviii.), Denys (*Arch. f. Exper. Path. Pharm.*, xx. 306), Kionka (*Arch. de Pharmacod. interend.*, 1898, v.).

† Schlesinger (*loc. cit.*) found after the division of the cord that the rise of arterial pressure caused by strychnine both absolutely and relatively exceeds that produced in the normal animal. This result we believe to have been due to imperfect section of the cord. For an elaboration of the reasons for this belief, see tenth edition of this treatise.

Our knowledge of the cardiac action of strychnine is still imperfect. Although Lahousse believes that in any dose strychnine depresses the intra-cardiac ganglia, it is probable that the small dose has a stimulating influence upon the heart. In the experiments of I. Steiner, confirmed by Klapp, it was found that strychnine affected the isolated frog's heart much more markedly when it was placed upon the posterior than when it was placed upon the anterior face ; also that it acted much more promptly and severely upon the separated sinus venosus than upon the separated ventricles or auricles, leading to the natural conclusion that it acts especially upon the ganglia of the sinus.

In regard to the action of the alkaloid upon the vagi there is much difference of statement by investigators. Carl Heinemann, Mayer, and Klapp all affirm that the heart under the influence of strychnine can be arrested by galvanization of the par vagum, but Martin-Magron and Buisson, E. T. Reichert and Lahousse,[21] state that the sufficient dose of strychnine paralyzes inhibition.* Reichert has found that the early effect of strychnine is to stimulate the peripheral inhibitory apparatus of the heart, but that if the dose have been sufficient this stimulation is followed by pronounced depression or even complete paralysis.†

Blood.—Harley found that blood shaken for twenty-four hours with air contained 11.33 parts of oxygen and 5.96 parts of carbonic acid ; while blood treated in a precisely similar manner, except in the addition of strychnine, yielded 17.80 parts of oxygen and 2.73 parts of carbonic acid. Kionka[22] found that blood taken from the strychnized animal does not absorb oxygen with the avidity of normal blood, although no spectroscopic changes could be discovered in it. Moreover, his analysis of blood gases shows during the dyspnœic stage of the poisoning an extreme lack of oxygen without any excess of carbonic acid. Maurel[23] states that five centigrammes of strychnine sulphate are sufficient immediately to kill the leucocytes in one hundred grammes of blood, and that in poisoning by strychnine sulphate the death of the leucocytes and of the animals takes place at the same time.‡

* For the paper of Brunton and Cash showing that strychnine increases the "refractory period" of the isolated frog's heart, see *Proc. Roy. Soc.*, 1883. A consideration of this memoir would require an elaborate discussion of the minute points of cardiac physiology, and, as it would throw at present no light upon the practical use of the drug, is not entered upon.

† According to Reichert, when the salt of strychnine is injected intravenously into the dog there is, first, a transient increase in the pulse-rate, due to the immediate overwhelming action of the undistributed strychnine upon the inhibitory apparatus of the heart; second, a lessening of the pulse-rate, due to slight stimulation of the pneumogastric endings; third, a marked increase in the pulse-rate, due to pneumogastric depression ; and, finally, a decrease in the pulse-rate, the result of an influence upon the heart-muscle or its ganglia. Reichert determined that five milligrammes of strychnine per kilogramme of weight will paralyze the peripheral vagi in the dog.

‡ The statement of Carl Heinemann, that the diminished frequency of cardiac movement and the diastolic pauses taking place in the heart of the strychnized frog occur after section of the vagi, of course does not disprove vagi stimulation by small doses of the drug. It is entirely possible that the strychnine may diminish cardiac frequency, partly by vagi stimulation, partly in another way.

Respiration.—The injection of strychnine produced in the dog an extraordinary increase in the respiratory air-movement, which in H. C. Wood's [24] experiments never amounted to less than seventy-five per cent., and sometimes rose to three hundred per cent. On chloralized dogs the respiratory effects of the alkaloid were even more pronounced.

Strychnine is among the most certain of the respiratory stimulants, its action upon the respiratory centres being evidently a portion of its wider influence upon the whole motor tract.

Temperature.—Although we know of no careful record of the temperature-curve in poisoning by strychnine in the human being, Kionka has shown that the primary elevation of the temperature which occurs in strychnine-poisoning both in man and the lower animals is in animals followed by a pronounced fall, which takes place even if the convulsions persist. During each period heat-production and heat-dissipation are above the normal, but during the rise of temperature the increase in heat-production is greater than the increase of heat-elimination, whilst during the period of falling temperature the overplus of heat-elimination is greater than that of heat-production. Kionka's observations are confirmed by the statement of Anton Obermeier,[25] that in the rabbit there is a notable increase in the production of carbonic acid,—*i.e.*, of oxidation,—as well as by the affirmation of U. Mosso,[26] that even in the curarized dog a very pronounced rise of rectal temperature may be produced by strychnine.* From these facts it would appear probable that strychnine increases heat-production not simply by increasing muscular action, but in some way independently of its convulsive action, although the convulsions must augment heat-production. The final fall of temperature is due to the excessive dissipation of heat, which in turn is probably the outcome of vaso-motor paralysis.

Eye.—The effect of strychnine upon the normal eye has been studied by Von Hippel [28] and Cohn,[29] with rather different results. They both, however, found the sharpness of vision increased.

SUMMARY.—In small therapeutic dose strychnine produces little apparent effect, but acts as a powerful bitter, increasing at the same time the general tone of the body. After large therapeutic doses there is probably a pronounced general stimulation and increase of bodily tone. The fullest permissible doses stimulate very powerfully the respiratory centres, and also slightly increase blood-pressure by stimulation of the vaso-motor centres, and probably also of the heart itself. Toxic doses produce violent reflex tetanic convulsions, without loss of consciousness, by causing such excessive irritability and excitement of the ganglionic spinal cells that these cells respond overwhelmingly to the slightest stimuli; they also lower the functional activity of the

* Denied, however, by M. C. Delezenne,[27] who states that in curarized animals the exhibition of strychnine is always followed by an abatement of the central temperature, which is often but not always accompanied by an increase in the temperature of the surface, which increase he explains by the supposition that the drug has the power of dilating the peripheral vessels.

motor nerve-trunks by producing exhaustion and by a direct paralytic influence. Death occurring during a convulsion is due to cramp asphyxia, and is usually immediately preceded by loss of consciousness; death between the convulsions is the result of a paralytic asphyxia, produced in part by an exhaustion, and perhaps also a direct or secondary paralysis, of the respiratory centres, and in part by a loss of functional power of the respiratory nerve-trunks; upon the cerebrum and upon the sensory nerves the alkaloid exerts no demonstrable influence, unless it be that it stimulates feebly the special sense centres. There is also reason for believing that the toxic dose paralyzes the peripheral pneumogastric nerve and greatly depresses the heart itself and the vaso-motor system. The ozonizing power of the red blood-corpuscles appears to be lessened by toxic doses of strychnine. The absorption and the elimination of strychnine are rapid, the alkaloid escaping partly in the form of strychnic acid and partly unchanged.

THERAPEUTICS.—Clinical experience shows that strychnine is a powerful bitter, tonic, and stomachic, stimulating digestion and increasing the appetite, a conclusion which has been elaborately confirmed by S. F. Hamper,[30] who, using Ewald's test-breakfast, found that the drug increases the volume and digestive power of the gastric juice as well as the movements of the stomach. Strychnine is, however, more than a mere stomachic : it is a most useful tonic when there are general relaxation and loss of nerve-power. A portion of its value probably arises from its action upon the spinal motor nerve-centres ; but in all likelihood it influences other portions of the cord, affecting the vaso-motor centres, and most probably also the trophic centres. Be these things as they may, strychnine is the best of all tonics in general *functional atony and relaxation.*

Many years ago Trousseau taught that in certain cases of *chorea minor* the strychnine preparations are very valuable, and Morris Benedict[31] asserts that the remedy is useful against choreic movements. It is not probable that in such cases strychnine exerts any specific influence. H. C. Wood has experimentally proved that in choreic dogs it greatly increases the activity of the movements ; and any good which it may achieve in chorea minor is probably due to its tonic powers.

The great influence of strychnine upon the function of voluntary motion early led to its use in cases of *paralysis*, often with the result of doing harm rather than good. It is very evident that it can be useful only when the paralysis is dependent upon, or at least accompanied by, a *depressed state* of the *spinal motor centres.* Whenever there is inflammation or irritation of these latter, strychnine may do great injury by increasing such irritation, and must never be employed. Like galvanism, in *hemiplegia* it can do only a very limited amount of good, and should not be exhibited until irritation from the clot has ceased. It is probably useful in many forms of *lead paralysis*, but when the symptoms resemble those of poliomyelitis—*i.e.*, when there is a multiple paralysis with rapid wasting of the affected muscles and alterations of the electro-contractility

—we have found strychnine pushed to the verge of poisoning extraordinarily efficacious.

The value of strychnine in *amaurosis* was first asserted by Nagel.[a] In atrophy of the essential nerve-structure little is to be expected from it or any other remedy. It is most useful in cases which have not yet reached the stage of atrophy, but present slight if any ophthalmoscopic changes. The chalky or greenish-white and cupped nerve-entrance is not always, however, sufficient cause for pronouncing the case hopeless, for these appearances are not sure indications of the amount of injury done to the axis-cylinders. Its value in amaurosis from abuse of alcohol and of tobacco is undisputed. In amblyopia from disuse,—as in strabismus and paresis,—after the parallelism of the visual axes has been restored, under its use normal sharpness of vision is much more rapidly attained. In cases in which the ophthalmoscope reveals but slight change in the retina and nerve,—*e.g.*, slight striation of retina around the disk, the margin of which is somewhat obscured, or in disturbances of the anastomotic circulation at the nerve-entrance, with or without diminished sharpness of central vision and contraction of the field,—strychnine is of marked benefit. The distressing headache and giddiness associated with these nerve-troubles which thus manifest themselves in the eye are frequently relieved by the use of strychnine, even though the nerve is quite atrophied and the eye blind. There is much difference of opinion as to the method of its administration, but better results in the hands of most observers follow its hypodermic use. The temple would seem to be a better locality than the arm, as improvement in the corresponding eye has been frequently observed, while its fellow remained as before. It should be given in gradually increasing doses, being governed by the tolerance of the action of the drug. Commencing with one-thirtieth of a grain, it can usually in a few weeks be carried up to one-tenth or even one-fifth of a grain once or twice daily, these doses causing only a twitching in the calves of the legs, or a slight sense of constriction about the throat, coming on in from ten to fifteen minutes after their administration, and subsiding in the course of an hour or two. It is necessary to maintain the physiological impression to insure the best results.*

For a discussion of the value of strychnine as a respiratory stimulant, see *Respiratory Stimulants*, page 268. The alkaloid is extremely valuable in acute or chronic diseases of the lungs whenever the respiratory function is failing. In long-standing *bronchitis* or *winter cough*, and in other obstinate pulmonic diseases with dilated right heart, the combination of strychnine and digitalis yields most excellent results. Much advantage may often be derived, especially in feeble subjects, by adding strychnine to ordinary cough mixture.

The value of strychnine in the treatment of the respiratory accidents

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* This paragraph was written by S. D. Risley.

of anæsthesia, which was first pointed out in the address of H. C. Wood before the Berlin Congress in 1890, is now universally acknowledged. The drug has no less value in other similar acute respiratory poisonings. Very frequently the best results are obtainable by using it in combination with other respiratory stimulants.

In *dyspepsia* or *constipation* or *diarrhœa*, connected with atony of the visceral muscular coat, strychnine is a very valuable remedy. In various local paralyses, such as *prolapse of the rectum*, *atonic retention of urine*, *atonic incontinence*, and *loss of voluntary motion* in certain groups of muscles from pressure upon or temporary injury of the supplying nerve, it may be very useful. There is reason to believe that it sometimes does good in these cases by influencing the nutrition of the affected muscle or the peripheral nerves; it should be injected into the affected part.

Strychnine is also a serviceable remedy as a stimulant in cases of mental and physical depression due to prolonged excitement and overwork. J. H. Musser[33] asserts that during the strain of student-life before examinations it is especially valuable in preventing the development of *asthenopia*.

Strychnine is an extremely serviceable remedy in the treatment of *cardiac diseases* with weakness of muscle. In mitral insufficiency we have seen it prolong life for years after the failure of digitalis, and when before its administration immediate death seemed inevitable. It should always be tried in cases of failing heart where digitalis disagrees, it not being possible at present to pick out those cases in which brilliant results are to be achieved by it. To be effective it must be given in rapidly ascending doses, the patient being kept, if necessary, for weeks and months on the verge of strychnine-poisoning, with distinctly heightened reflexes and some muscular stiffness. Clinical experience shows that it has no cumulative action, but that the patient becomes accustomed to its use, so that a grain a day may finally be given without any serious effects. In acute *narcotic poisoning*, in serious *respiratory diseases*, in chronic *alcoholism*, and in *plumbic poliomyelitis*, whenever strychnine is used for a very decided immediate effect much larger doses should be employed than have been heretofore used. These doses should be given hypodermically at intervals of from four to six hours, under the immediate care of a trained nurse or other equally skilful person, who should vary the dose according to the effect produced. In chronic *neurasthenia* excellent results are sometimes obtained by slowly ascending doses carried over a period of one or two years.

Toxicology.—Sufficient has already been said in regard to the general symptoms of strychnine-poisoning. It only remains to discuss the diagnosis.* This is especially important, because strychnine is frequently

* A lesion found in one case by Moriz Rosenthal may possibly be characteristic. It consists of numerous small cross-rents in the heart-muscle, accompanied by small extravasations (*Nervenkrankheiten*, 1870, 334).

used criminally, and because not rarely it is impossible for the chemist to detect it after death.

The only disease with which a typical case of strychnine-poisoning seems to be readily confounded is tetanus, in its various forms of idiopathic, traumatic, infantile, and hysterical. Cases of strychnine-poisoning have, however, occurred in which the symptoms have appeared to point towards some cerebral disease or cerebral poisoning. Thus, in the case reported by Henry Pilkington,[34] the patient was found unconscious, surrounded by vomited matters, with excessively uneven pupils and an elevated temperature. After death both lateral ventricles were found to contain clots, and there can be little doubt that the high arterial pressure during an early convulsion had produced an apoplexy which was the cause of the subsequent symptoms and death. It has been asserted that in fatal cases the duration of the attack will always distinguish between natural tetanus and that produced by poison. Louis Starr,[35] however, reports traumatic tetanus fatal in twelve hours after the first muscular twitchings, and within one hour and a half after the first convulsion ; and death from tetanus has occurred fifteen minutes after the reception of the injury (Jaccoud[36]).

The following table shows, we think, in as clear and brief a manner as possible the differences between traumatic or idiopathic tetanus (No. 1), hysterical tetanus (No. 2),* and strychnic poisoning (No. 3). The references in column No. 3 are to authorities who affirm that the symptoms there given are peculiar to poisoning :

No. 1.	No. 2.	No. 3.
	Commenced with blindness and weakness.	Begins with exhilaration and restlessness, the special senses being usually much sharpened.† Dimness of vision may in some cases be manifested later, after the development of other symptoms; but even then it is rare.
Muscular symptoms usually commence with pain and stiffness of the back of the neck, sometimes with slight muscular twitchings; come on gradually.	Muscular symptoms commenced with rigidity of the neck, which gradually "crept over the body," affecting the extremities last.	Muscular symptoms develop very rapidly, commencing in the extremities, or the convulsion, when the dose is large, seizes the whole body simultaneously.‡
Jaw one of the earliest parts affected; rigidly and persistently set.	Jaw rigidly set before a convulsion, and remained so between the paroxysms.	Jaw the last part of the body to be affected : its muscles relax first, and, even when during a severe convulsion it is set, it drops as soon as the latter ceases.§

* Column No. 2 is from an actual case. See trial of Mrs. Wharton, *New York Medical Record*, 1873.

† Taylor, *On Poisons*, 683; Wormley, *Micro-Chemistry of Poisons*, 536.

‡ Wormley, 536; Stillé, *Therapeutics*, ii. 148.

§ Taylor, *On Poisons*, 134, 682; Wormley, 536, 540, 541; Tardieu, *Sur l'Empoisonnement*, 924.

No. 1.	No. 2.	No. 3.
Persistent muscular rigidity, very generally with a greater or less degree of permanent opisthotonos, emprosthotonos, pleurothotonos, or orthotonos.	Persistent opisthotonos, and intense rigidity between the convulsions; and after the convulsions had ceased the opisthotonos and intense rigidity lasted for hours.	Muscular relaxation (rarely a slight rigidity) between the convulsions, the patient being exhausted and sweating. If recovery occur, the convulsions gradually cease, leaving merely muscular soreness, and sometimes stiffness like that felt after violent exercise.*
Consciousness preserved until near death, as in strychnic poisoning.	Consciousness lost as the second convulsion came on, and lost with every other convulsion, the disturbance of consciousness and motility being simultaneous.	Consciousness always preserved during convulsions, except when the latter become so intense that death is imminent from suffocation, in which case *sometimes* the patient becomes insensible from asphyxia,† which comes on during the latter part of a convulsion, and is almost a certain precursor of death.
Draughts, loud noises, etc., produce convulsions, as in strychnic poisoning.	Desired to be fanned.	The slightest "breath of air" produces a convulsion.‡
May complain bitterly of pain.	Crying-spells, in which he "sobbed violently," and "cried like a child," alternated with the convulsions.	Patient may scream with pain, or may express great apprehensions, but "crying-spells" would appear to be impossible.
Eyes open, rigidly fixed, during the convulsion.	Eyes closed.	Eyes stretched wide open.§
	The spasms in the leg must have been partial, as the feet were crossed and toes inverted, which could not happen if all the muscles were involved, because the muscles of eversion, being very much the stronger, would of necessity overcome the antagonistic muscles, and the feet be everted.	Legs stiffly extended, with feet everted,‖ as the spasms affect all the muscles of the leg.

Death from strychnine in man and other mammals mostly occurs in a convulsion, and under these circumstances is undoubtedly due to asphyxia, caused by the unyielding, spasmodically contracted muscles. In man, death sometimes occurs not in a paroxysm, but during relaxation, and probably then is the result not only of the exhaustion following effort, but also of the direct action of the poison upon the respiratory centre and nerves.

In frogs, death must occur from other causes, since a frog, as shown by Claude Bernard, will live for days after removal of its lungs, probably by breathing through its skin. The causes of death in the frog are not hard to find when the physiological action of the drug is known. The lymph and true hearts (Kölliker, Harley[87]) are very much affected, but the chief factor is no doubt paralysis of the motor nerves.

* Taylor, *On Poisons*, 134, 136, 682; Wormley, 536, 540, 541; Tardieu, 924, 938, 939; Husemann, *Handbuch der Toxicologie*, 168.

† Wormley (1st ed.), 536; Taylor, *Medical Jurisprudence*, 331, 332; Wharton and Stillé, *Medical Jurisprudence*, paragraph 757; Tardieu, 923; Stillé, *Therapeutics*, 148.

‡ Stillé, *Therapeutics*, 148.

§ *Ibid.*; Wormley, 536; Tardieu, 924.

‖ Tardieu, 924; also other authorities, which we have neglected to note, and at present writing have not at hand.

Honigmann[38] reports a remarkable case, in which acute inflammation of the kidneys followed strychnine-poisoning.

The minimum fatal dose of strychnine is probably something under half a grain; the latter quantity has several times caused death, once in a man in twenty minutes;[39] one-third of a grain given at intervals in fractional doses has produced such alarming symptoms as to indicate that in a single dose it might readily destroy life; one-hundredth of a grain is said to have killed a child three and a half months old;[40] but ten grains (Tschepke[41]), twenty grains (A. E. Connor[42]), also twenty-two grains (George Gray[43])—taken on a full stomach and retained two hours—have failed to cause death, in each case probably on account of slow absorption.

In treating poisoning by strychnine, a chemical antidote should be at once administered, such as tannic acid or iodine or one of its soluble salts. As, however, the compounds formed in the stomach by these substances are not permanent, theoretically a quick emetic may sometimes be advisable. Potassium permanganate has the power of oxidizing strychnine, but its value as a practical antidote has not as yet been determined. For the lessening of the excitability of the spinal cord various spinal depressants have been from time to time recommended. No spinal depressant, however, which, like aconite or tobacco, is also powerfully depressant to the circulation, should be used. The remedies which may be employed are potassium bromide, chloral,* chloroform, and amyl nitrite. Alcohol has been strongly recommended by some authorities (Amagat, Stacchini) as antidotal; and when the great muscular relaxation of drunkenness is remembered, it seems very probable that the commendation has some basis. Husemann has, however, shown that alcohol can scarcely be looked upon as a real antagonist to the alkaloid.

The best treatment of strychnine-poisoning is apparently to be found in the conjoint use of chloral and potassium bromide, with, when convulsions are very threatening, inhalations of amyl nitrite or chloroform. Half an ounce of the bromide with half a drachm to a drachm of chloral may be given at once in a severe case; and, if necessary, every twenty minutes afterwards two drachms of the first and fifteen grains of the second remedy may be exhibited.

Chloroform or amyl nitrite should be given by inhalation whenever the convulsions are extremely severe, and if the patient cannot swallow, a drachm of chloral may be injected into the rectum, or, especially where respiration is very seriously affected, five minims of amyl nitrite may be given hypodermically. It is essential to remember that any disturbance of the patient may, when the symptoms are well developed, bring about a fatal convulsion. Thus, we have seen death occur in a convulsion caused by an effort to get the mouth open to give a remedy. Hence, unless the case is seen in the beginning, no attempt should be

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* For detailed discussion of the relations of strychnine and chloral, with account of experiments by various investigators, see tenth edition of the present treatise.

made to evacuate the stomach. Artificial respiration, which has been highly commended by some, cannot, we believe, ever be of service in human poisoning.

It is evident that the convulsed muscles will often resist such efforts as are usually made to force air into the lungs of man as successfully as they do the unassisted struggles of nature; and Harley states that he has found artificial respiration of no use whatever in animals. On the other hand, Leube, in an apparently very careful series of experiments, found that artificial respiration has great influence in saving or prolonging life, according to the amount of the poison ingested. In his experiments, the dose which ordinarily produced convulsions did not do this so long as artificial respiration was kept up; and the "lethal dose" did not kill if artificial respiration was maintained for four hours, although opisthotonos was induced in some cases. Jochelsohn[44] only succeeded in prolonging life, but Rosenthal, according to Husemann, obtained similar results to Leube, and M. Schiff[45] has, in a series of experiments, corroborated in the main facts the results of the German investigators, although disagreeing with them in minor particulars. He found that animals in which *forcible* artificial respiration was maintained survived doses much larger than those ordinarily fatal. The artificial respiration was performed by inserting a canula into the trachea and filling the lungs by force. Klapp also found artificial respiration of service. None of the ordinary methods of artificial respiration in man are, however, sufficiently powerful to be of any value.

ADMINISTRATION.—As a tonic, strychnine sulphate may be given in granule in doses of from one-fortieth to one-twentieth of a grain (0.0016–0.0032 Gm.). Whenever it is desired to push the remedy to its physiological limit, it should be given hypodermically in ascending doses until restlessness, general excitement, muscular twitching, stiffness of the neck or legs, or other symptoms are manifested. In many cases of palsies, especially with trophic changes in the muscles, the best effect seems to be obtained by injecting the strychnine salt directly into the affected muscle. If proper antiseptic precaution be taken, hypodermic injections do not cause local irritation.

BRUCINE.—Strychnine clings so closely to brucine that the physiological actions attributed to brucine may be in truth caused by contaminating strychnine. L. Wintzenreid[1] found that brucine acts as a stimulant to the spinal cord and a paralyzant to the motor nerves, but does not influence the cerebrum or the sensory nerves; and that in the higher animals, at first it increases the arterial pressure and afterwards lessens it, in large doses paralyzes the vagi, causes death by asphyxia, and in other ways acts like strychnine. The more recent experiments of Lauder Brunton[2] are in accord with the results obtained by Wintzenreid in showing that brucine causes spinal convulsions in mammals when injected directly into the circulation. Brunton found, however, that when taken by the mouth it produces no symptoms, probably because it is excreted as rapidly as it is absorbed. In an elaborate study, Edward T. Reichert[3] reached the conclusion that the physiological action of brucine is precisely that of strychnine, except that brucine is much less rapidly absorbed, is from forty to fifty times less powerful as a convulsant, is more poisonous to the sensory nerves, and is more uncertain in its effect upon

bodily temperature. Further, brucine appears to have an action upon the volitional centres of the frog different from that of strychnine, producing a brief period of motor paralysis preceding the stage of spinal convulsion (Mays, Reichert).* Thomas I. Mays[4] found that brucine locally applied to the nerves of the frog rapidly produces a paralysis of the sensory fibres. This led him to test it as a local anæsthetic in man, and he asserts that a five or ten per cent. solution applied to the mucous membrane of the mouth caused rapid loss of sensibility; also that a twenty per cent. solution applied to the back of the hand caused pronounced impairment of sensibility. Mays used this solution with excellent results for the relief of the itching of chronic *pruritus*. Ralph W. Seiss[5] and Charles H. Burnett have found that the application of a five per cent. solution in the local pruritus of inflammation in or about the external ear usually gives very marked relief. Burnett states that his results were far more satisfactory than those which he has obtained with cocaine. In using brucine as a local anæsthetic it is essential that it be chemically pure: the *nitrate* or the *sulphate* may be selected, and one drop of hydrochloric or sulphuric acid should be added to the solution for each three grains of the alkaloid salt.

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* For a research showing the comparative action of strychnine and brucine on different species of frogs, see Sautesson (*Archiv f. Exper. Path. u. Pharm.*, xxxv.).

FAMILY VI.—DEPRESSO-MOTORS.

UNDER this heading are considered certain drugs which are used for the purpose of lessening the activity of the spinal cord. They have, except in this particular, but little in common in their action, and must be studied individually.

PHYSOSTIGMA—CALABAR BEAN. U. S.

An irregular, kidney-shaped bean, about an inch in length and three-fourths of an inch wide, the product of the Physostigma venenosum, a perennial woody creeper of Calabar, Africa, where the bean has been used by the natives as an ordeal test for criminals, witches, etc., since time immemorial. It contains an alkaloid known as *physostigmine*, or *eserine*. E. Harnack and L. Witkowski[1] have described a powerful tetanizing alkaloid, *calabarine*, which is sometimes abundant in commercial extracts of Calabar bean. As Harnack has produced it from physostigmine, it is probably a decomposition product from that alkaloid (see also Husemann[2]).

PHYSIOLOGICAL ACTION.—*Local Action and Elimination.*—No apparent irritant action occurs from therapeutic doses of Calabar bean or its alkaloid.

Both absorption and elimination are very rapid. N. Teich and D. Schweder[3] have both found physostigmine in the urine half an hour after its ingestion. Although the alkaloid has been detected in various secretions by Dragendorff and his pupil Pauder, it chiefly escapes through the kidneys. Its effect upon the urinary secretion has never been studied, excepting in that Merson[4] states that it decreases the excretion of urea and other urinary solids in *paresis*.

General Action.—No sensible effects are perceptible after the full therapeutic dose of Calabar bean, except it be slight weakness and dislike for muscular exertion. The symptoms produced by large doses are giddiness, lessened heart-action, great muscular weakness, with, in most cases, contraction of the pupil, and sometimes vomiting, and still more commonly purging, which may be very free. A pupil of Gubler took 0.15 grain of eserine sulphate, and suffered, after a time, nausea, giddiness, and intense muscular weakness, so that he could not stand; three-quarters of an hour afterwards he vomited some of the solution mixed with bile, but his strength did not begin to return for two and a half hours.

When an animal receives a small fatal dose of Calabar bean, after a time muscular tremors appear, and almost immediately the victim falls to the ground, or lies down, in a state of perfect muscular flaccidity. The pupils generally contract,

and the respirations become slow, irregular, and often stertorous. All reflex actions are almost at once diminished, and this diminution grows greater and greater, until it ends in their complete abolition. So long as the condition of the motor system allows of it, evidences of sensibility are manifested whenever the animal is in any way injured. According to Clementi Papi,[5] the voice is completely lost. The muscular tremors persist during the whole period of paralysis, and, indeed, even after cessation of the respiration. They vary greatly in intensity, and in some cases are so severe (Fraser) as to simulate general convulsions. As the minutes go by, the rhythm of the respiration becomes more and more affected, and at last death takes place quietly, consciousness being preserved until the last few gasping respirations close the scene.* The pupils sometimes, but not always, dilate immediately after death. According to the experiments of Fraser, the bodily temperature is slightly elevated.

After a small lethal dose of the poison, the fatal result is always due to failure of the respiration, and if the body be at once opened the heart is found still beating; indeed, it has been seen to continue to do so for one and a half hours after death (Fraser). If a very large amount of the drug be given, the animal falls almost at once, paralyzed, with only a few muscular twitchings. The pupils contract, and in a very short time the gasping respiration ceases. The heart is now found distended and passive, but often will contract under the stimulation of a galvanic current.

Nervous System.—Upon the cerebrum physostigmine has no perceptible influence. The paralysis and loss of reflex activity which it produces are undoubtedly due to a depressant action upon the motor cord. Thus, Fraser, Harnack, Witkowski, and others have found that if in the frog a peripheral nerve be protected by tying its artery and the batrachian be poisoned with Calabar bean, the paralysis in the protected limb occurs *pari passu* with that in the remainder of the body. Again, Fraser divided the spinal cord of a frog, and then cut or tied all the blood-vessels going to the posterior section of it. After this, the animal was poisoned with physostigma, and while the usual symptoms developed themselves in the anterior portion of the body, reflex actions were unaffected in the posterior part. Further, Fraser[6] has found that when the poison is applied directly to the cord, fibrillary contractions, due probably to a local irritant influence, are induced in the muscles supplied from below the point of application, but in a little while all movements cease, and even galvanization of the cord itself is unable to elicit response. It is asserted by several investigators that the extremely minute dose of physostigmine acts as a stimulant to the spinal cord. Although this may be true, it seems at present writing improbable.†

* Köhler, Rossbach, and others have affirmed that Calabar bean produces a tetanic intoxication. A plausible explanation of these singular observations, and of many of the discrepancies of authorities, is to be found in the discovery of calabarine. Its discoverers state that it produces first a violent tetanus, and afterwards paralysis. It is plain how its presence in varying amounts in Calabar bean preparations would modify their action. The researches of Köhler, of Vintschgau, and of Rossbach and Fröhlich are especially open to doubt, on account of their statements that Calabar bean tetanizes. It is very probable that the extracts used by them contained a notable percentage of calabarine.

† Papi states that in frogs the stage of exaltation and reflex activity precedes the stage of depression. M. Vintschgau (*Stitzungsb. Math. Nat. Classe Akad. Wissen. Wien.*, 1867, Bd. lv., Abth. ii. 49) affirms that in a frog whose iliacs he had tied the poison produced violent convulsions, which affected the protected legs, and must, therefore, have been of central origin. Two plausible explanations of this suggest themselves: *first*,

Nerves.—Although there is reason for believing that physostigmine is capable of affecting both motor and sensory nerve-trunks, yet this action is so feeble as probably to take no part in the production of symptoms. The afferent nerves are less sensitive than the efferent, since Fraser has found, first, that the local application of a strong solution of the poison to a nerve kills the efferent or motor fibres before the afferent or sensory, although the functions of both of them are finally abolished; second, that when the arteries in the left leg of a frog are tied, and the animal poisoned both with Calabar bean and strychnine, there comes a time when reflex movements are excited in the left leg by irritation of the right foot, although irritation of the left foot does not cause movements in the right leg,—*i.e.*, the impulse is able to travel up the poisoned nerve of the right leg but not down it.

The extreme feebleness of the influence of physostigmine is shown by the fact that the frog's nerves are often active after death from Calabar bean (Laschkewich,[7] Vintschgau,[8] and Fraser); and Fraser has determined that after the fatal result has been produced rapidly with physostigmine, the rate of conduction of impulse is as rapid in the nerve to which the poison has had free access as in one which has been protected by the tying of its artery.

Loss of power in the motor nerves after poisoning by Calabar bean has been found in the frog only, and, further, only when the dose has been so small that the heart has continued to beat long after the cessation of respiration, so that the nerves had been, as it were, macerated in a solution of the poison. Harnack and Witkowski deny that physostigmine has even this feeble influence upon the nerve-trunks. The loss of power is probably in the termination of the nerve rather than in the trunk, for Fraser found that when all the blood-vessels supplying the gastrocnemius muscle were cut in a frog and the animal poisoned, at a certain time irritation of the crural nerve produced spasms of the gastrocnemius alone.

Muscles.—The continuance of the muscular movements after death indicates that they are due to a direct action of the drug upon the muscles. This conclusion is established by the experiments of Laschkewich, of Fraser, and of Leven and Laborde.[9] All of these investigators have noted that after death these contractions are increased by exposure to the air and by direct stimulation of the muscles; and Fraser has found that they occur in the frog during life after section of the supplying nerve, and also in a muscle actually cut out of the body. Laschkewich has confirmed the latter fact in the case of warm-blooded animals, and Leven and Laborde have proved that previous destruction of the lower end of

that the physostigmine used contained calabarine or other active impurity; *second*, the well-known fact that certain spinal depressants produce convulsions, or even excite reflex action, by paralyzing reflex inhibition, or in some unknown way. The probability of the impurity of the alkaloid is increased by the assertion of Harnack that Merck's "calabarinum purum" contains little or no calabarine. Schweder, however, asserts that pure physostigmine, in small doses, acts as a distinct stimulant to the cerebral, respiratory, and vaso-motor centres.

the spinal cord in a guinea-pig does not prevent the development of the muscular twitchings in the hind legs. Schweder contends that the action of the poison is not, however, upon the muscular structure itself, but upon the peripheral nerve-endings in the muscle, basing his conclusions especially upon the asserted fact, that previous hypodermic injections of atropine or curare prevent the development of rigidity in the snake poisoned with physostigmine. It is certain that the final paralysis produced by Calabar bean is not of muscular origin, since at the time of death the contractility of the muscles is in no way diminished, but, on the contrary, Fraser has noted that loss of contractility and rigor mortis are greatly delayed in Calabar-bean poisoning.

Circulation.—In the mammal, after therapeutic and even toxic doses, the cardiac action of physostigmine is subordinate to its influence upon the nerve-centres; but, as has been shown by Fraser, when overwhelming doses of the poison are administered, especially if they be injected into the jugular vein, death results from syncope, or from consentaneous failure of the cardiac and the respiratory functions, and the heart is found arrested in diastole, flaccid, but, according to Fraser and to C. Arnstein and P. Sustschinsky,[10] responding, though feebly and uncertainly, to direct stimulation. In the poisoned frog the early contractions of the heart are slower and more forcible than the normal (Harnack and Witkowski); whilst the arrested heart is insensible to stimuli (Rossbach and Fröhlich[11]).

When smaller doses of the poison are exhibited, there is slowing of the heart's action (Laschkewich, Fraser, and J. Tachau[12]). Although, according to the experiments of Fraser, there is at first a slight fall of the blood-pressure, which is probably due, as he believes, to diminished pulse-frequency, yet, in spite of the continuance of the slow pulse, the arterial tension soon recovers itself, and remains for a long time much above the normal point, while at the same time the individual cardiac beats are greatly increased in strength (Fraser, Bezold and Götz*). Finally, the arterial pressure falls far below normal, and the power of the heart is gradually extinguished.

That the rise of arterial pressure must be largely the result of a stimulant action upon the heart or upon the vessel-walls is shown by the finding of Bezold and Götz, that the arterial pressure still rises under the influence of physostigmine after high-up section of the spinal cord; and by that of Harnack and Witkowski, that when the vaso-motor centres are paralyzed with chloral, physostigmine causes a very decided increase of the arterial pressure. The facts—that section of the vagi does not interfere with the production of the cardiac phenomena of Calabar bean, and that in the frog physostigmine acts in its usual way on the heart, although the brain and medulla have been destroyed (Vintschgau); also that

* We have not seen the original paper of these authorities in the *Centralblatt für Med. Wissenschaft*, 1867, but quote them from the paper of Arnstein and Sustschinsky.

when physostigmine is placed directly on the heart, or into one of its chambers, it causes a long diastolic pause, followed by contractions, interrupted by pauses, and finally by resumption of regular contractions, or else by diastolic arrest, the heart still retaining its power of responding in an embarrassed manner to stimuli (Fraser)—would appear to demonstrate that physostigmine directly affects the heart. How far this influence is upon the cardiac ganglia and how far upon the muscle-fibre has not been determined. It seems, however, probable that physostigmine affects the cardiac muscles in the same way as it does the muscles of voluntary life.

There is, however, much reason for believing that physostigmine affects the peripheral inhibitory apparatus, although the evidence is not entirely clear. Arnstein and Sustschinsky found in rabbits and also in guinea-pigs that the influence of galvanic irritation of the vagi upon the heart is much greater after than before poisoning with physostigmine, diastolic arrest being produced much more easily and continuing much longer than normal after the withdrawal of the stimuli. Moreover, after having completely paralyzed the peripheral cardiac vagi in the rabbit by large doses of atropine, they restored functional power to these nerves by injections of Calabar bean. If the accuracy of these experiments be admitted, it must also be admitted that physostigmine is a powerful stimulant to the peripheral cardiac inhibitory apparatus. Köhler, however, using the frog, and Rossbach and Fröhlich, using the rabbit, failed to resuscitate the atropinized vagi by means of Calabar bean, but a negative result in such a case might be due to an improper proportion in the doses of the counter-poison, or to the atropine being employed in overwhelming amount.

Physostigmine appears to have no paralyzing effect upon the vagi ; at least in warm-blooded animals these nerves are never paralyzed (Fraser, Arnstein and Sustschinsky, Harnack and Witkowski) ; and the loss of functional power which has been detected by Fraser, Rossbach and Fröhlich, Harnack and Witkowski, in the vagi of the frog does not appear until so long after the cessation of respiration that it is very probably a secondary result.

That Calabar bean does not affect the cardiac inhibitory centres would seem to follow from the experiments of Arnstein and Sustschinsky, in which an injection of the drug through the carotid into these centres failed to affect at once the rate of the heart.

The question as to the effect of physostigmine upon the blood-vessels cannot at present be positively answered. Evidence concerning it has been brought forward by Fraser and Harley in the form of observations made upon the web of the frog. We have already stated our belief that this sort of evidence is of very little value. In the present instance, as usual, it is entirely contradictory as given by different observers. (For details, see tenth edition of this treatise.)

The fact that the rise of arterial pressure produced by physostigmine

after section of the cord is not nearly so great as in an uninjured animal suggests, but does not prove, that the drug affects the vaso-motor centre. Analogy makes it probable that the muscular fibres in the coats of the vessels share the wide-spread muscular action of the poison, and that the peripheral contraction of the arteries is an efficient cause in producing rise of blood-pressure. In considering the general physiological action of the drug, it must not be forgotten that its influence upon the heart is entirely subservient to its influence on the nervous system,* and that death in the mammal occurs before the stage of cardiac palsy is reached, unless the drug be injected directly into the heart in overwhelming dose.

Blood.—According to Fraser, after death from physostigmine the blood coagulates slowly and loosely, and the red disks present various irregularities of outline; it is probable that these changes are due to the long asphyxia, and that the poison does not directly affect the blood.

Intestines.—Intestinal peristalsis is primarily much increased by the action of Calabar bean (Westermann,[13] Papi, Fraser). After poisonous doses there is at first a stage of exceedingly active movements in the bowels; then spasmodic tetanic contraction of the intestines occurs, so that their calibre is very much diminished; and finally relaxation and dilatation take place. After death the vermicular movements are found very much lessened (Fraser) or altogether abolished (Tachau). The action of Calabar bean upon the intestines appears to be peripheral, due to contact of the poison in the blood with the muscular fibres or the nerve-elements in the walls of the bowels; for Westermann found that extirpation of the cardiac ganglion had no effect upon the action of the drug, but that tying of the mesenteric and of the cœliac arteries, before poisoning, prevented any increase in the peristalsis.

Secretion.—Calabar bean probably increases intestinal secretion. Its action upon the salivary glands is often decided, and, according to Heidenhain, is not prevented by atropine.

Eye.—The contraction of the pupil which is produced by Calabar bean is, without reasonable doubt, caused by a local peripheral influence. The fact that physostigmine will contract the atropinized pupil is relied upon by Schmiedeberg[14] to prove that the action of physostigmine is directly upon the iris muscle; a deduction which seems unwarranted. As well argue that atropine acts upon the muscle because it antagonizes physostigmine.

The closeness of the analogy between the pupillary action of atropine and that of physostigmine is seen in the fact that, like the former, the latter, as shown by the experiments of Vée and Leven[15] on chickens, does not affect the irides of birds. It is probable that the two alkaloids are directly antagonistic in their action upon the peripheral nerve-endings in the pupil.

It has been held by various authorities that if galvanization of the sympathetic

* For a discussion of the peculiar cardiac relations of physostigmine and muscarine, see the paper by Harnack and Witkowski. Those authors believe that Calabar bean sets in motion the heart arrested in diastole, not by paralyzing the cardiac inhibitory apparatus, but by stimulating the cardiac muscle.

fibres in the neck fails to expand a contracted pupil, the myosis must be due to paralysis of the sympathetic. Evidently, however, this is asserting too much, for, as pointed out by Grünhagen,[16] it is conceivable that an oculo-motor spasm can exist of such intensity that the antagonistic nerve is unable to dilate the pupil. The testimony as to whether galvanic stimulation of the sympathetic does or does not dilate the physostigminized pupil is somewhat conflicting. Grünhagen says that dilatation always occurs, although to a slight extent (*in beschränkten Masse*) ; while, on the other hand, Gustav Engelhardt[17] has found that galvanization of the cervical sympathetic has no effect upon the physostigminized pupil. The experiments of Fraser, of Bernstein and Dogiel, and of Rosenthal[18] would seem to reconcile these differences, and, by their accord, to prove that under the maximum influence of Calabar bean the sympathetic is powerless, while when the contraction is the result of a milder influence of the drug, stimulation of the cervical nerve will cause a certain amount of dilatation.* Fraser, and also Engelhardt, have found that if the poles of a battery be applied directly to an iris even most profoundly contracted by physostigma, immediate dilatation occurs.

If it be true that direct stimulation of the muscle-fibres of the iris causes dilatation of the physostigminized pupil, whilst stimulation of the sympathetic nerve fails of effect, it would appear that Calabar bean *paralyzes the sympathetic nerve-endings in the iris.* On the other hand, the well-known force of the myosis indicates that it is not due simply to loss of power in the dilating fibres ; an indication which is corroborated by the fact that section of the cervical sympathetics will not produce a myosis as complete as that caused by physostigmine. It would seem, therefore, that the whole influence of Calabar bean is a simultaneous stimulation of the oculo-motor nerve-endings and paralysis of the peripheral sympathetic nerve-endings.

The observations of Rossbach and Fröhlich, that overwhelming doses of physostigmine finally dilate the pupil, have been confirmed in cases of human poisoning (see Leibholz). It would seem, therefore, that when the alkaloid is in sufficient amount the primary oculo-motor stimulation is followed by oculo-motor palsy.

SUMMARY.—The dominant physiological action of Calabar bean is a persistent depression of the motor centres of the spinal cord, involving also the respiratory centres in the medulla, and producing loss of reflex action with an increasing paralysis, ending in death from centric paralytic asphyxia. Contraction of the pupil is usually seen in the poisoning, and is always produced by the local application of the drug; it is due to a peripheral influence and probably to paralysis of the sympathetic nerve-filaments with stimulation of the oculo-motor nerve-endings. The motor nerve-trunks are scarcely affected, but in slow poisoning probably suffer some depression of function which especially affects their peripheral endings. Neither the cerebral cortex nor the sensory nerve nor the sensory nerve-centres are acted upon, unless secondarily in the latest stages of poisoning. Calabar bean acts as a

* More recently Rossbach and Fröhlich affirmed that galvanization of the sympathetic still causes dilatation, even when the action of the physostigmine is most vigorous. As it is scarcely conceivable that the various other investigators should have been so much in error, it is probable that Rossbach and Fröhlich used such strong currents that they were directly transmitted to the iris.

stimulant directly either upon the muscle structure itself or upon the peripheral nerve-endings in the muscles. The influence of the drug upon the circulation is entirely subordinate. Early in the poisoning there is a rise of the blood-pressure, which is in great part, if not altogether, due to a direct stimulation of the cardiac muscle or its contained ganglia, although it is probable (not proved) that there is some contraction of the blood-vessels, which may be due to an influence upon the muscle-fibre in the vessel-walls similar to that upon other muscle-fibres, striated and non-striated. We have no information as to the effect of the poison on the vaso-motor centre. According to some authorities, the peripheral vagi are strongly stimulated. Intestinal peristalsis is greatly increased by the direct action of Calabar bean upon the muscular fibres or the peripheral nerve-endings in the intestinal walls. The alkaloids of Calabar bean are rapidly absorbed, and are eliminated chiefly by the kidneys.

THERAPEUTICS.—The physiological action of Calabar bean has suggested its use in spasmodic affections, in atony of the muscular coats of the bowel, and in various diseases of the eye.

The action of Calabar bean upon the spinal cord very early led to its use in spasmodic affections, and especially in *tetanus*. In the paper of B. Roemer[19] are collected forty-seven cases, of which twenty proved fatal. To these we are able to add the twenty whose references are given below,* making in all sixty-seven cases, with thirty-seven recoveries and thirty deaths,—not a very flattering record.

It is, however, proper to state, as affecting the value of these statistics, that much of the Calabar bean extract which has been offered in the market is practically inert, and in all probability in some of these cases the drug did not have a fair trial; and that when especial care was taken by certain observers better results were achieved, although on so small a scale as to leave the issue in much doubt.†

In *trismus neonatorum*, Calabar bean has been employed with results certainly no more encouraging than those obtained in tetanus. In *chorea* it has also been used by some practitioners with asserted advantage, but further experience hardly justifies its administration.[20]

The physiological action of physostigmine upon the unstriped intestinal muscle-fibres has led to its employment in *atony* of the muscular coat of the bowels and other similar organs. V. Subbotin[21] has used the extract

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* FATAL CASES.—Fenwick, one (*Glasgow Medical Journal*, 1869, 300); Franzolin, one (*The Doctor*, Oct. 1, 1871); Laborde, one (*British Medical Journal*, June, 1872); Valdivieso, one (*Philadelphia Medical Times*, i. 455); Tyson, one (*Ibid.*, 418); Johnson, one (*Ibid.*, 372); one (*London Lancet*, 1874); Silbermann, one (*Charier's Thesis*, 1881); Delamarre, one (*Paris Thesis*, 1875); Richelot, one (*Thèse de Concours*, 1875). RECOVERIES.—Fenwick, one (*Glasgow Medical Journal*, 1869, 300); Newman, one (*Medical Examiner*, July, 1869); W. W. Keen, one (*Philadelphia Medical Times*, i. 195); J. H. Packard, one (*Ibid.*, 138); Cunningham, one (*British Medical Journal*, i. 1874); one (*Cincinnati Lancet*, Sept. 1878). All these cases were of the traumatic form of the disease. Charier, one (*Paris Thesis*, 1881); Burnam, one (*Lancet*, Jan. 1881); Pooley, one (*New York Med. Journ.*, Sept. 1878); Silbermann, one (*Charier's Thesis*, 1881).

† For a favorable record, see Watson (*Glasgow Medical Journal*, N. S., 1869, i. 54); consult also *London Practitioner*, Sept. 1869.

with the happiest results in a case of *chronic bronchial catarrh* with intense *dyspnœa*, believed to be due to weakness of the bronchial muscular fibres, and also in one of apparently "*phantom tumor*," with *chronic intestinal dyspepsia* and *catarrh*. In *constipation* dependent upon relaxation, and as an addition to laxative pills, we have found it very useful. A. Hiller[22] strongly endorses the value of the extract in *chronic intestinal atony*, after or during a catarrh, in the convalescence from fever, etc., and in *constipation* with flatulence, in *meteorism*, etc.

Calabar bean has also been employed in *strychnine-poisoning*, and a recovery obtained after the ingestion of three grains of the latter alkaloid is reported by J. W. Keyworth.[23]

In *epilepsy*, some trials have been made of the drug, but its value is very doubtful. Harnack and Witkowski have found that in epileptic guinea-pigs physostigmine causes a succession of fits lasting for hours and days. They have further noted a similar influence upon man. Attention has also been called to the employment of Calabar bean as a *galactagogue*,[24] the extract being applied to the breast itself.

ADMINISTRATION.—Calabar bean is usually administered as an extract (EXTRACTUM PHYSOSTIGMATIS, U. S.), the commencing dose of which is one-tenth to one-fifth of a grain (0.0065–0.013 Gm.). The dose of the tincture (TINCTURA PHYSOSTIGMATIS—fifteen per cent., U. S.) is twenty to forty minums (1.25–2.5 C.c.). The alkaloid is preferable, on account of its certainty. The salicylate (PHYSOSTIGMINÆ SALICYLAS, U. S.) is preferable to the sulphate (PHYSOSTIGMINÆ SULPHAS, U. S.) as more permanent, the sulphate being very deliquescent. The thirtieth of a grain (0.002 Gm.) of either the alkaloid or its salt may be considered to be the full dose.

TOXICOLOGY.—So far as we know, Calabar bean has not been used, either in Europe or in this country, with criminal intent. In Liverpool seventy children were accidentally poisoned at one time.[25] Many of the victims vomited spontaneously, and thus relieved themselves. Those brought to the hospital were in a state of extreme prostration and muscular relaxation. They appeared to suffer almost no pain, some of them, however, saying that they had a "belly-ache." Among some thirteen examined, one had the pupils contracted. The only child who did not recover was excessively weak, and, crying out suddenly, was dead of syncope. The heart was found relaxed and flabby, both sides equally full of blood. Half a bean produced in a strong man[26] great muscular weakness, tightness across the chest, temperature of 96.6° F., very slow, intermittent, irregular pulse, and collapse, without vomiting, purging, contraction of the pupils, or abdominal pain. Lodderstaedt[27] reports a hypodermic injection of one-half a milligramme of the physostigmine sulphate in a boy nine years old, followed in a quarter of an hour by violent headache, free sweating, salivation, slowing of the pulse, repeated vomiting, contraction of the pupils, and, finally, deep collapse, from which, however, the patient recovered. Two girls took between

them 0.1 gramme (1.53 grains) of physostigmine, with the result of sudden unconsciousness, great redness of the face, muscular relaxation, vomiting, widely dilated, immovable pupils, and, on recovery of consciousness, violent abdominal pains, with pulse 60, and hard; recovery after some hours (Leibholz[28]).

In 1864 Kleinwächter first used successfully atropine in Calabar bean poisoning, and thereby started much discussion and research.

Bourneville[29] detailed in 1867 some experiments which seemed to show that there is a real antagonism between Calabar bean and the mydriatic, and in 1870 published five experiments upon guinea-pigs, which were very decisive in that a proved fatal dose of physostigmine was given in each case and recovery obtained by the use of non-lethal doses of atropine. In 1869 Roberts Bartholow, of Cincinnati, on the strength of a few really indecisive experiments, arrived at a conclusion opposite to that of Bourneville.

In an extremely thorough research, which might well serve as a model to any one studying the antagonistic action of poisons, Fraser[30] demonstrated that within certain limits atropine may be relied upon as a counter-irritant poison to physostigmine. He found that in the rabbit one-fiftieth of a grain of atropine could successfully antagonize one and a half but not twice the minimum fatal dose of Calabar bean, one-fortieth of a grain of atropine could overcome two to two and a half times the minimum lethal dose of physostigmine, and three-fiftieths was sufficient for three times the minimum fatal dose. When four times the lethal dose of physostigmine was given to the rabbit, atropine was powerless to do good. In all these cases the atropine was given just before the administration of the Calabar bean. When the atropine was given five minutes after the physostigmine the largest dose of the physostigmine which could be combated successfully was three times the minimum fatal dose. No experiments were made by Fraser to test the value of physostigmine in atropine-poisoning. These experiments of Fraser[30] have been in some degree confirmed by the imperfect researches of Amagat.[31]

The antagonism between physostigmine and pilocarpine is at least as great as that between atropine and pilocarpine. (See article on Jaborandi.) The practical deduction from the scientific and clinical evidence is that in any case of Calabar bean poisoning both of the antagonistic alkaloids should be used in doses proportionate to the amount of the poison ingested.

POTASSII BROMIDUM—POTASSIUM BROMIDE. U.S.

Potassium bromide occurs in milk-white cubic or quadrangular prismatic crystals of an acrid saline taste, freely soluble in water and slightly so in alcohol. When its solution is mixed with starch, and chlorine is added, a yellow color is developed. A bluish tint betrays contamination with an iodide.

PHYSIOLOGICAL ACTION.—*Local Action.*—When a solution of the bromide is applied locally to the heart, it produces instantly marked lessening of its action, and, if in sufficient amount and concentration, even instantaneous diastolic arrest.[1] Upon the voluntary muscles it acts in a similar manner when similarly applied. If its solution be not too concentrated or abundant, however, the muscle of the frog is first thrown into a tetanic spasm, and Purser suggests that the tetanic symptoms seen

in the frog poisoned by potassium bromide are due to this action on the muscles. On the nerve-trunks, and also on the nerve-centres, the bromide acts, when applied locally, as a paralyzing poison (Amory,[2] Ringer and Morshead[3]). It is, therefore, evident that potassium bromide in sufficient quantity is a poison to all the higher animal tissues. In general poisoning of animals by hypodermic injection of the bromide, this local action is often very manifest, and paralysis of the part into which the solution has been thrown follows very rapidly upon the injection.

Potassium bromide is distinctly irritating, and when in the form of powder it is affirmed to be somewhat caustic, and has been highly recommended for the destruction of excessive granulations, etc.

Absorption and Elimination.—Potassium bromide is freely absorbed and circulates in the blood as the bromide. Elimination takes place to a certain extent through the skin, and probably largely through the intestinal mucous membranes, though the chief avenue is the kidney.

P. Guttmann[4] has recognized bromine in the contents of the acne pustules of bromism; Bill[5] detected the bromide in marked quantities in the fæces of men taking it; and H. Quincke[6] found that when forty grains of sodium bromide were given to dogs with intestinal fistula, two and a half hours afterwards the intestinal juices were free from the bromide, which reappeared in them three to six hours later. The salt has been found by Voisin, Amory, Namias, Bill, etc., in the saliva and in the urine, and by Amory[7] in the perspiration. In the body of a man who died while taking it, M. Namias[8] found it in all the liquids, as well as in the brain, liver, spinal cord, lungs, etc. The rapidity of elimination seems to vary: thus, Amory recovered one-half of the amount ingested during the first, and one-third during the second, twenty-four hours, and Ware (Thesis of H. P. Bowditch) obtained a little more than half of the amount ingested in the urine of the succeeding thirty-two hours, while Bill was not able to get more than one-eighteenth of it during the first day. Bill has frequently found the bromide in the urine two weeks after the last dose had been exhibited; and Rabuteau has seen its presence persist under similar circumstances for a month.

Clinical results show that when the bromide is given continuously in full doses it accumulates in the system. Under these circumstances it undoubtedly is to be found in every tissue of the body, but, according to Doyon and Cazeneuve[9] (confirmed by Féré and Herbert[10]), it is stored up in the nerve-centres much more largely than elsewhere.

General Action.—Potassium bromide administered to frogs in minute doses produces as a first result a tetanoid condition, in which there may be very marked opisthotonos. After a short time this stage of muscular excitement gives way to one of great muscular relaxation and total abolition of reflex actions. Voluntary movements, however, often occur during this period, and the frog which has been lying limp and apparently dead will startle the observer by a sudden vigorous leap. This fact has been so frequently witnessed that there can be no doubt of its truth.*

* It is vouched for by the following observers: J. M. Purser (*Dublin Journ. Med. Sci.*, 1869, xlvii. 324); Lewisky aus Kazan (*Virchow's Archiv*, 1869, xlv. 191); J. V. Laborde (*Archives de Physiol. Norm. et Pathol.*, 1868, i. 423, and *Comptes-Rendus*, 1867, lxv.); Damourette and Pelvette (*Bull. Thérap.*, 1867, lxxiii. 249).

Very early in the paralytic stage the respiratory movements are affected, and they gradually grow less until their final arrest. When a very large dose of the bromide is given, death may be induced by paralysis of the heart (Albert Eulenberg and Paul Guttmann[11]); but after a small toxic dose this viscus continues to beat long after the cessation of breathing. If the drug be given by an injection practised in the vicinity of the heart, sudden cardiac arrest always occurs.

Upon mammals[12] (Eulenberg and Guttmann[11]) the bromide acts very much as upon frogs, inducing progressive paralysis, depression of temperature, and death by asphyxia when given in small poisonous doses; and great disturbance of the circulation, with finally diastolic arrest of the heart, when very freely administered.

So far as we know, no fatal case of acute poisoning by potassium bromide is on record. In our own experience an ounce taken by mistake by a young adult produced violent pain in the œsophagus, nausea with a little vomiting, great thirst, feeling of weight in the head, and excessive sleepiness, which lasted for three days. In a case reported by Dougall[13] an ounce and a half taken within twenty-four hours was followed by coma, with weak pulse, cold extremities, temperature 96.8° F., total abolition of the reflex action, and general cutaneous anæsthesia, followed by excessive drowsiness interrupted by periods of talking delirium and by periods of rationality, the symptoms gradually subsiding during a fortnight.

The results of the continuous employment of large doses of the bromide, however, demonstrate that it acts upon man as upon the lower animals. When it is taken with sufficient freedom to accumulate in the system, a conjunction of phenomena known as *bromism* arises. The cerebral symptoms are a sense of mental weakness, heaviness of intellect, failure of memory, partial aphasia, great somnolence, and depression of spirits. With these there may be decided impairment of the sensibility of the mucous membranes and of the skin, so that titillation of the fauces may be without effect, and, according to Puche, even heat applied to the skin calls forth no complaint; Huette[14] has seen in some cases absolute anæsthesia of the sclerotic conjunctiva. The sexual function is abolished. There are also very generally fetid breath and an eruption of acne which may indeed be very severe. Of course, in any individual case of bromism many of these symptoms may be wanting; but when the use of the remedy is persisted in, they all at last become developed in an intense degree. In the words of Edward H. Clarke:

"The fetid breath becomes nauseous; œdema supervenes on congestion of the uvula and fauces; the whispering voice sinks into aphonia; sexual weakness degenerates into impotence; muscular weakness becomes complete paralysis; reflex, general, and special sensations disappear; the ears do not hear, nor the eyes see, nor the tongue taste; the expression of hebetude becomes first that of imbecility, then that of idiocy; hallucinations of sight and sound, with or without mania, precede general cerebral indifference, apathy, and paralysis; the respiration, without

the stertor of opium or alcohol, is easy and slow; the temperature of the body is lowered; as the bromism becomes more profound, the patient lies quiet in bed, unable to move or feel or swallow or speak, with dilated and uncontractile pupils, and scarcely any change of the color of his skin or face."

Death has been attributed to the continuous use of the bromide in large doses. Thus, Hameau reports the case of a young woman who took four and a half pounds during the course of ten months, and while in a condition of cachexia, with yellowish skin, a copper-colored eruption upon the forehead, colic, gastralgia, insomnia, etc., suddenly became greatly prostrated, and had delirium with profuse sweats, followed by death in four days. Anton Eigner[15] details the case of a woman who took five pounds in less than a year, and while having very pronounced symptoms of bromism was seized with delirium and suffered from hallucinations of sight and hearing, saying that she was being poisoned, and finally died of pneumonia. In neither of these cases can it be considered probable that the bromide was the direct cause of death.

Nervous System.—The persistence of voluntary movement in the frog after the abolition of reflex actions shows that the influence of the drug is not chiefly exerted upon the cerebral centres of motor impulse, nor upon those cells of the cord which originate movement, but upon either the afferent nerves or those portions of the cord which transmit the impulse from these nerves to the cells presiding immediately over motion. This is confirmed by some experiments of Lewisky, in which it was shown that previous separation of the cord from the cerebrum had no influence upon the action of the bromide. Both he and Purser[16] also found that death occurred from small doses before the motor nerve-trunks and the muscles had lost their irritability (confirmed by Saisson[17]). This being so, the question arises whether the paralysis be spinal or due to paralysis of the peripheral afferent nerves. There is an apparent conflict in the evidence upon this point. Eulenberg and Guttmann found that when access of the poison was prevented to one or more limbs by tying the arteries, reflex actions were abolished in these parts as rapidly as in others. Similar results have been obtained by Lewisky,[18] by Roberts Bartholow,[19] by Purser,* and by Laborde.[20] The latter observer has also found that electrical stimulation of a nerve high up will cause violent spasms in the muscles directly supplied by it, although it may be unable to excite the slightest reflex tremor. On the other hand, Damourette and Pelvette assert a contrary result. Unfortunately, they do not give the details of their experiments. They state, however, that if the lumbar plexus of vessels be tied before the poisoning, the fore feet lose their reflex activity before the hinder. There are two possible methods of reconciling their results with those of the other observers. In some way the operation may have interfered with the circulation in the lower part of the cord, and

* From the wording of his memoir, however, it is doubtful whether Purser performed the experiment himself.

consequently the poison have reached more freely the upper part of it and acted first upon it. Again, if the injection was, as is very probable, thrown into the anterior portion of the body, the poison may have reached the anterior extremities in so concentrated a form as to have acted, as it were, locally upon their nerves and muscles. The same observers in another portion of their memoir show that the solutions of these salts in the frog travel rapidly by imbibition ; and this and their local action seem to us to be the cause of the differences of experimental results. It seems well established that cutaneous anæsthesia in greater or less degree accompanies the loss of reflex activity ; for, as Purser says, a poisoned animal quite able to jump submits to pinching, pricking, burning, etc., without moving. Eulenberg and Guttmann have seen the same thing in some rabbits. Damourette and Pelvette[21] have noticed a condition in which electrical stimulation of a nerve-trunk produced marked reflex action, although no excitement of the skin supplied by the afferent fibres of the nerve was capable of doing this, showing that the extremities of the sensitive nerves are affected before the trunks. The evidence is, we think, sufficient to prove that potassium bromide affects all parts of the nervous system of the lower animals, but that the cerebrum, the motor tract of the cord, and the efferent nerves are the last portions to be affected ; that the most sensitive to its action is the receptive portion of the cord,—that which receives and transmits reflex impulses,—and next to this, and perhaps almost equally susceptible with it, are the peripheral ends of the afferent nerves.

Upon the cerebrum of the higher animals the bromides undoubtedly exert an influence, and the researches of Albertoni[22] have thrown much light upon the usefulness of the drug in epilepsy. That observer found that when administered to dogs the bromide depresses very markedly the power of the motor zone of the cerebral cortex to respond to stimuli, and to give forth, on decided irritation, epileptic discharges ; it was also discovered that this action of the bromide was much more decided when there had been a prolonged saturation of the system with the drug than after a single large or even toxic dose. The intellectual symptoms of bromism show that in man the action of the bromide on the cerebral cortex is more marked than in the lower animals, on account, no doubt, of the higher cerebral development. The drug in other respects acts upon man as upon lower mammals, lowering the reflex excitability of his spinal cord, paralyzing the ends of the peripheral nerves, etc.

According to the researches of B. Schulze,[23] there is under the influence of the bromide a decided decrease in the elimination of phosphorus,—an indication that the protoplasmic molecular changes in the nervous system are lessened by the drug.

Circulation.—It is well established that large toxic doses of the bromide exert a direct paralyzing action on the heart, lessening both the force and the frequency of the beat, and finally causing diastolic arrest.* J. G.

* For experiments upon the isolated frog's heart, see *Med.-Chir. Trans.*, 1882.

Schouten [24] found that during the slow injection of a two per cent. solution into the vena cava of a rabbit the cardiac systole grew slower, the diastolic pauses longer, and finally the heart stood still, exhibiting only fibrillary contractions of its walls. The same observer is, so far as we know, the only one who has made manometrical studies of the action of small doses of the drug. He found that such amounts of the bromide administered hypodermically or by the stomach always produced increased pulse-frequency with lessened arterial pressure.

It would appear, therefore, that even small doses of potassium bromide are directly depressant to the circulation. The fall of the arterial pressure is certainly largely of cardiac origin. It is probable, though not proved, that the vaso-motor system also shares the paralyzing influence of the drug. How far the base in potassium bromide is responsible for the cardiac action has never been determined.

At one time it was generally taught by authorities that potassium bromide causes vaso-motor spasm, and that the nerve symptoms produced by it are secondary to this spasm. At the time of the writing of this work this view was so widely and firmly held as to require careful consideration. At present it is, however, believed by no one, and the reader is therefore, for a discussion of it and the objections to it, referred to the tenth edition of this treatise. It is sufficient to state that there is no proof that the small dose of the bromide produces vaso-motor spasm, and that there is positive proof that the nervous symptoms are produced by a direct action of the drug upon the tissues concerned.

Temperature.—In warm-blooded animals, toxic doses of potassium bromide lower very decidedly the temperature. There have been no calorimetric experiments to determine whether this fall of temperature is due to a diminished heat-production or an increase in heat-elimination. The relaxed condition of the vaso-motor system under the influence of the bromide favors the escape of heat, and it is probable that the fall of bodily temperature is due in part or altogether to an excessive loss of heat.

Nutrition.—The symptoms of bromism show that potassium bromide has a distinct influence upon the general nutrition of the body, and it would appear probable that on account of the potassium in it there would be an increase in tissue-waste. The results reached by investigators are, however, distinctly conflicting, although in many ways they appear to be the *a priori* expectation.

It should be further recognized that we have no knowledge whatsoever as to the general influence of bromine upon the tissue-changes.

Rabuteau [25] found that while taking the bromide there was slight lessening in the daily elimination of urea. The experiment was, however, a single one, and the daily dose of the bromide was only fifteen grains, an amount so small as to have no determinate influence. H. Bill, in an elaborate study of the action of the bromides upon elimination, determined that there was a very decided decrease in the amount of carbonic acid thrown off from the lungs, but that the elimination of urea

was not sensibly affected. On the other hand, the quantity of urine was usually increased, the coloring-matters invariably augmented, and the action on phosphoric acid varied: after smaller doses it appeared to be slightly increased. Schulze, whose article we have seen only in abstract, in an apparently very careful investigation on his own person, found as the result of the ingestion of one hundred and fifty grains of bromide a day that the urinary secretion was greatly increased, the phosphorus diminished, the sulphur very much increased, and the nitrogen slightly increased. The experiments of Chittenden and Culbert[26] were made with the maximum dose of one hundred and fifty grains a day. They found diminished excretion of phosphorus, but a pronounced increase of urea. In Chittenden and Culbert's experiments ammonium bromide acted like potassium bromide, but more powerfully, so far at least as the urea was concerned.*

SUMMARY.—When in sufficient concentration potassium bromide acts as a powerful depressant upon all of the higher tissues. It is absorbed rapidly and eliminated in all the secretions more slowly; so that when given continuously it accumulates and causes *bromism*, usually first manifested by fetid breath, acne eruption, sleepiness, muscular relaxation, and general depression. The portions of the human organism most sensitive to its influence are the whole cerebral cortex, the receptive side of the spinal cord, and the afferent peripheral nerve-endings. The influence of potassium bromide upon the circulation is subordinate to its action on the nervous system. In full dose, however, it is directly depressing both to the heart and to the blood-vessels, and we have no knowledge that it acts in any dose as a stimulant either to the heart or the vaso-motor system. The fall of temperature which has been noted, chiefly in the lower animals, after toxic doses of the bromide is in all probability due to extreme heat-dissipation, in turn the outcome of vaso-motor depression.

THERAPEUTICS.—Potassium bromide is employed by the therapeutist to quiet *cerebral excitement* when not inflammatory in its nature; to lessen over-susceptibility of the spinal centres of reflex action, or of the peripheral afferent nerves which lead to these centres; and to subdue nervous excitement of the genital system.

The bromides are contra-indicated by an excessive irritability of the gastro-intestinal mucous membrane; when such condition exists they may provoke exhausting diarrhœa. Great exhaustion, and especially great nutritive exhaustion of the nerve-centres, is a contra-indication to their use. Thus, owing to the excitement that attends *confusional insanity*,—*i.e.*, the insanities following child-birth, typhoid fever, surgical operations, etc.,—bromides are frequently administered in large doses, to

* It has been asserted (Binz, *London Pract.*, 1874) that potassium bromide owes its physiological and therapeutic powers solely to its base. This is plainly not the case, as the bromide is not largely decomposed in the system, and the symptoms caused by it are very different from those produced by potassium carbonate: in a later publication (*Arch. f. Exper. Path. Therap.*, xiii.) Binz himself has shown that bromine vapor produces in frogs effects in many respects similar to those caused by the potash salt. At the same time it is almost certain that the potash influences the system to some extent. G. Krosz (*Arch. f. Exper. Path. Therap.*, vi. 43), in three experiments upon man, found decided difference in the results produced by proportionate doses of potassium bromide and of sodium bromide. He attributes the lessening of reflex activity to the bromine (see also Steinauer, *Virchow's Archiv*, lix.).

the great detriment of the patient. We are well convinced that under such circumstances they greatly lower the nutrition and check recovery. In the same way, in *cerebral softening*, *senile dementia*, and allied disorders, they must be used, if at all, only with the greatest reserve.

There are various forms of *nervous excitement*, or unrest, such as sometimes follow excessive intellectual toil, anxiety, and other nervous strain, or occur during convalescence from acute disorder, in which the salt now under consideration is very valuable. The same may be said of some forms of *hysteria*. In some cases of *neuralgia* the bromide affords great relief, but in the majority of cases it fails. It has seemed to us useless in neuralgia dependent upon anæmia or want of power; and our experience agrees with that of Anstie, that it is especially useful in persons of good nervous power, muscular force, and activity of circulation. As an hypnotic, it is employed in wakefulness from nervous excitement and in *delirium tremens*, but is of very feeble power.

The chief use of the bromide is to lessen motor activity. It is especially in *epilepsy* that it has attained a well-deserved reputation, doing far more good than all other remedies combined, sometimes apparently effecting cures, more commonly ameliorating the symptoms, but occasionally failing entirely. There is no known method of distinguishing before trial with any certainty in what cases it will do good. The assertion of Trousseau, that it is least efficient in the mild form of the disorder known as *petit mal*, accords with our experience. The most brilliant results have, as a rule, been obtained in cases of not too long duration in which the fits were frequent and severe. The governing principle in its use is to try it in every case, increasing the dose until a mild degree of bromism is induced, and being guided by the results.

The salt is also often efficacious in various reflex spasmodic neuroses: in the *vomiting* of *pregnancy* or of *uterine diseases;* in the gastric *convulsions* of children; and, according to J. T. Rothrock, in preventing the so-called *urethral fever* induced in very susceptible males by the introduction of the catheter or bougie, it is very useful. The physiological action of the salt seemingly indicates that it is one of the remedies best suited for the treatment of *tetanus*. Clinical experience certainly accords with this conclusion: in a table published in previous editions of this treatise were collected thirty-four cases of tetanus, nearly all traumatic, treated chiefly by potassium bromide, with but four deaths. Not less than a half-ounce of the salt should be exhibited in the day, and at night chloral should be used as an hypnotic. (See CHLORAL.)

In *strychnine-poisoning*, Saisson has demonstrated the value of the bromide by experiments on animals, and Charles B. Gillespie[27] and C. L. Bard[28] have each reported, under its use, recovery without vomiting after the ingestion of three grains of the alkaloid.

In nervous excitement connected with the *genital function*, potassium bromide is often of value. When there is actual inflammatory disease, as in *gonorrhœa*, the drug frequently fails to effect the desired end.

If, however, there be no organic lesion of the organs or of their nerve-centres, the continued dose will usually succeed to a greater or less extent. We have found the remedy effective in cases of semi-impotence from over-irritability of the organs causing emission too soon during attempted sexual congress. There is abundant evidence as to its value in *nymphomania*. As an adjuvant to other physical and moral measures of relief, the salt may be used with satisfaction in men suffering from *masturbation*. In nervous symptoms occurring at the time of the menopause or complicating uterine disease, and in the peculiar train of morbid phenomena arising from the forced suppression of the sexual function in vigorous individuals of either sex to whom circumstances have denied marriage, the bromides have almost a "unique power."

Ch. Bernard[39] affirms that potassium bromide in doses of from twenty to forty-five grains a day removes with marvellous quickness *malarial enlargements* of the *spleen*.

ADMINISTRATION.—We have known half an ounce of the bromide to be taken at once without inducing any serious symptoms; and in severe acute cases, as in tetanus and strychnine-poisoning, it is perfectly safe to administer two-drachm doses at short intervals, as the case may require. Almost all the indications for the use of the bromide are best met by the so-called continuous dose,—*i.e.*, by the administration of so much in the twenty-four hours until an effect is induced. In epilepsy, from one to two drachms (4–8 Gm.) may be exhibited daily (see page 239); although as little of the remedy as will suffice to prevent the recurrence of the fit must be used, yet any amount necessary to do this should be given, unless distinct bromism be produced before the paroxysms are arrested. The remedy must be exhibited in a freely diluted solution. In some cases it causes diarrhœa, which may generally be checked with small doses of opium. It is essential in epilepsy and other chronic disorders to persist in the continuous administration of the bromide, it may be for years; and it is remarkable how rapidly the symptoms of long-continued bromism subside upon the withdrawal of the drug.*

AMMONII BROMIDUM—AMMONIUM BROMIDE. U.S.

Ammonium bromide may be obtained in colorless crystals, but generally occurs in a granular powder, which becomes yellowish on exposure. It has a saline, pungent taste, and is readily soluble in water, sparingly so in alcohol. When mixed with mucilage of starch, if chlorine-water be added it becomes yellowish brown; a blue tint would indicate the presence of iodine.

PHYSIOLOGICAL ACTION.—The physiological action of ammonium

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* Ch. Féré asserts that many of the disagreeable symptoms of bromism are due to its disturbance of the alimentary canal, and are prevented by the daily exhibition of four grammes of beta-naphtol and four grains of bismuth salicylate, which doses are borne for months without any inconvenience, usually with much benefit to the appetite and digestion (*Nouv. Iconog. de la Salpètr.*, 1890).

bromide has not as yet been fully investigated ; but our present knowledge indicates that in many points it resembles that of the corresponding salt of potassium, whilst in others it differs from the latter. According to N. Bistroff[1] when two decigrammes are administered to a frog, a period of quietude and lessened irritability is induced, which, after fifteen or twenty minutes, gives place to violent tetanic convulsions. Later, all excitability is lost, so that even burning calls forth no recognition ; the frog lies in whatever position it is placed in, the spasms become more violent, and death ensues. Similar phenomena have been witnessed also by Amory[2] in the rabbit and the guinea-pig, although in one of Amory's experiments the guinea-pig died without convulsions having been noted. The curious abolition of reflex action and of sensibility consentaneously with the occurrence of violent convulsions was noted frequently, and death seems always to have resulted from asphyxia. In the experience of Bistroff, moderate non-fatal doses produced only weakness and uncertain movements in the rabbit.

Ammonium bromide appears to exert very little influence upon the peripheral motor apparatus. Amory has seen the nerves retain their power of conduction after having been placed in a "strong solution ;" and, according to Bistroff, muscles retain their irritability after soaking five minutes in a ten per cent. solution. According to the latter observer, the heart always continued beating after death from the drug, and the heart removed from the batrachian and laid in a ten per cent. solution did not in any degree lose its normal activity. Even a twenty per cent. solution dropped upon the bared heart produced only a momentary arrest of the ventricular systole. On the other hand, Purser asserts that the heart is soon arrested in diastole in poisoning by this salt, and that the nerves and muscles also lose their irritability sooner than after poisoning by potassium bromide.

The subject certainly needs further investigation ; yet it seems to us probable that ammonium bromide exerts less influence upon the cardiac and other muscles than does potassium bromide, but that in other respects their actions are very similar. The experiments of Amory indicate that the ammonium salt affects temperature and acts on the capillaries in the same way as that of potassium, and that it is also eliminated in a similar manner. The experiments of Bistroff show that in the cat, at least, ammonium bromide has no especial influence, as has been asserted, upon the superior laryngeal nerves.

THERAPEUTICS.—Ammonium bromide is capable of fulfilling all the indications for which potassium bromide is used, and is especially useful in *epilepsy*. (See *Strontium Bromide.*)

SODIUM BROMIDE, U. S., closely resembles in appearance potassium bromide, and has been supposed by Voisin to have very similar physiological and therapeutic properties. On the other hand, M. J. V. Laborde[1] states that in double the toxic dose of potassium bromide he has found

that it does not produce any characteristic symptoms in the frog, the guinea-pig, or the dog, and leaves the animal perfectly healthy.

By clinicians the drug has been used to a considerable extent. Meredith Clymer[2] asserts that it will arrest epilepsy without producing the unpleasant cerebral symptoms of bromism. He gives twenty grains three times a day. Hammond[3] asserts that in epilepsy it is in no wise superior to the potassium salt, but affirms that its hypnotic power is much greater. M. E. Decaisne,[4] as the result of the trial of the drug in twenty-seven cases (*epilepsy*, *chorea*, *hysteria*), asserts that its action is the same as that of the potassium salt, except that instead of causing diarrhœa it constipates. Notwithstanding this testimony, our own experience is in accord with the physiological teachings, that sodium bromide, although not free from therapeutic value, is not equal to potassium bromide in subduing nervous excitation, and is in no wise superior to it.

LITHIUM BROMIDE, U. S., was, we believe, first employed in medicine by Gibb,[1] who recommended it as gently toxic and sometimes diuretic. He used it in very small doses. Attention was first called to its employment in nervous affections by S. Weir Mitchell,[2] who stated, as the result of his experience, that, when administered to the amount of half a drachm to one drachm daily, it acts in some cases of *epilepsy* after potassium bromide has failed, and that it is generally efficient in about one-half the dose of that salt; also that its hypnotic action is much more decided. Clark confirms these observations; but, according to our experience, the drug has no especial value.

STRONTII BROMIDUM. U. S.—*Strontium bromide* occurs in colorless, odorless, very deliquescent crystals of a bitter saline taste, soluble in 1.05 parts of water. Strontium bromide shares the action of the other strontium salts upon the alimentary canal and of other bromides upon the nervous system. It is therefore an extremely useful remedy in the treatment of epilepsy. It yields its bromine, however, rather slowly to absorption, and we have found that it usually acts much better in conjunction with ammonium bromide than it does by itself. The mixture of the two bromides, also, is much better tolerated than is the ammonium bromide alone; so that after long trials in many hundreds of cases of epilepsy we have reached the conclusion that the best possible results are in the majority of cases to be obtained by the administration of a mixture containing in each dose twenty grains of ammonium bromide, ten grains of strontium bromide, five grains of antipyrin, and three minims of Fowler's solution, given morning and evening. In individual cases the dose of the bromides in this mixture is to be increased or decreased, the intent being to use as small an amount of the bromides as possible to control the paroxysms, and under no circumstances to go beyond the production of mild bromism. As the bromides act by accumulation in the system, and as patients become very much disgusted by the long continuance of

frequent doses, it is usually much better to give the drug in two large than in three smaller doses a day.

HYDROBROMIC ACID.—A solution of the gaseous compound of bromine and hydrogen in water was first employed as a therapeutic agent by Wade.[1] E. T. Reichert[2] found that moderate doses caused some temporary elevation of the blood-pressure, which Reichert attributes —without, apparently, sufficient evidence—to vaso-motor spasm of peripheral origin. Large doses were directly paralyzant to the heart and to a less extent to the voluntary muscles. Reflex action is suspended by the acid in the frog, and all portions of the spinal cord and nerves are depressed by the poison ; but Reichert presents experimental facts which indicate that the sensory portions of the cord and the sensory nerves are affected before the motor system by hydrobromic acid as they are by the bromides. A long series of trials made by H. C. Wood with hydrobromic acid in the Epileptic Wards of the Philadelphia Hospital determined that the official acid in equivalent doses acts very much as does potassium bromide, but is distinctly more irritant to the stomach, and less apt to produce an eruption of acne or muscular depression. It may be used alone in the treatment of *epilepsy*, but the combination of it with the bromide has seemed to us the best form of administration : the large dose required, when it is given by itself, in most cases distinctly irritates the stomach. Under all circumstances it must be well diluted. The official dilute hydrobromic acid (ACIDUM HYDROBROMICUM DILUTUM, U. S.) represents in each drachm nine grains of potassium bromide, and may be given in one-half to one-fluidounce doses in a tumblerful of sweetened water (15–30 C.c.).

GOLD BROMIDE.—Goubert asserts that the gold bromide is the most successful of the bromides in the treatment of *epilepsy* and the more severe forms of *migraine*, having a more permanent effect than the other preparations ; and Shtcherbak, in a series of experiments upon the lower animals, found that the gold bromide in doses of 0.1 to 0.2 gramme to the kilogramme had a very pronounced effect in inhibiting the cortical motor centres. The alleged superior activity of the gold bromide can hardly be dependent solely upon the bromine in it, since Shtcherbak found that it was about six times as strong as the potassium bromide in its action upon the psycho-motor centres, although it contains only 55 per cent. by weight of bromine, whilst the sodium bromide contains 77.7 per cent. and the potassium salt 67.2 per cent. Goubert gives it to the adult in doses of eight milligrammes ($\frac{1}{8}$ grain), gradually increased to twelve, administered in dilute solution. In our own limited trials a grain a day of the gold bromide has failed to cause any symptoms or perceptibly to influence the recurrence of epileptic attacks.

Two bromine compounds which have been used to a slight extent in medicine, but have failed to establish themselves as valuable remedies, are *bromal hydrate* and *bromoform*.

Bromoform was proposed by Bonome and Mazza, and has been used as a general anæsthetic, but certainly has no advantage over the better known anæsthetics, and is probably more dangerous. W. Gerhardi[1]* has shown that bromoform is capable of producing wide-spread fatty degeneration in the lower animals.

For a *résumé* of the physiological action of bromal hydrate, which is certainly valueless as a practical medicine, see the tenth edition of this treatise.

AMYL NITRIS—AMYL NITRITE.† U.S.

Amyl nitrite was discovered by the French chemist Balard in 1844, and the attention of physiologists was called to it in 1859 by Guthrie; but it was not until 1865 that Richardson, of London, introduced it to the notice of the profession. It is a yellowish, oily, very volatile liquid, of a very penetrating, persistent, fruity odor. It is prepared by the action of nitric acid on amylic alcohol, or, as it is commonly called, fusel oil.

PHYSIOLOGICAL ACTION.—*Local Action.*—Amyl nitrite has no irritating properties. It causes a progressive loss of functional power in every highly organized tissue with which it comes in contact. Nerve-centres, peripheral nerves, muscles of organic and voluntary life, all succumb to it alike. If the contact be not continued too long, the tissue may recover even after a total suppression of its function,—a proof that the poison exerts no destructive chemical or devitalizing influence upon the tissues, such as that of sulphuric acid or veratria.

Absorption and Elimination.—Amyl nitrite is absorbed with extraordinary rapidity, especially through the lungs, and must also be eliminated from or destroyed in the system with great rapidity on account of the fugaciousness of its action. F. Rohrmann[1] believes that the nitrites undergo oxidation in the system, because he has found that when potassium nitrite is administered to the lower animals it appears in the urine as potassium nitrate.

General Action.—The most prominent symptoms induced when amyl nitrite is inhaled by a man in moderate quantities are a sense of great fulness and distention of the head, amounting at last to severe pain, and accompanied by intense flushing of the face, a deep, labored respiration, and an exceedingly rapid, violent action of the heart. The succession of these phenomena is usually so rapid that often they seem to be simultaneous; but it is said that the cardiac disturbance is sometimes very distinctly

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* See also *Wien. Med. Jahrb.*, 1883, 497. For poisoning, see *Times and Register*, 1892; also *Annals of Gynæcology*, 1896-97; *Pest. Med.-Chir. Presse*, 1897.

† *Bertoni's ether* or *tertiary amyl nitrite*, a mixture of amyl nitrite and iso-butyl nitrite, has been found by Lauder Brunton and T. J. Bokenham to act very much as does the ordinary amyl nitrite, except that its effects are somewhat more slowly developed and are more permanent. It is not proved to be more stable than the ordinary amyl nitrite and has no advantages over the latter. According to Dunstan, amyl nitrite of commerce is chemically a mixture of α and β amyl nitrites, iso-butyl nitrite, ethyl nitrite, and propyl nitrite (*St. Bartholomew's Hospital Report*, 28, 1892).

manifest before the other symptoms. It has been noticed by Peck and confirmed by Ladendorf that objects look yellow to a person fully under the influence of the drug. After poisonous doses the symptoms have been great pallor, usually dilatation but sometimes contraction of the pupils, excessive muscular relaxation, slow, scarcely perceptible pulse, hæmoglobinuria, and irregular respiration.

In the lower animals the first stage of the action is like that just described in man. After this the breathing becomes violently hurried and panting, progressive muscular weakness and diminution of reflex activity ensue, and finally death from failure of respiration, sensation and consciousness being preserved almost to the last. A very peculiar symptom is that a long time before death both the arterial and the venous blood become of a nearly uniform chocolate color. Convulsions are sometimes present ; but in our experience more often the animal is exceedingly quiet throughout the poisoning.

Nervous System.—The influence of amyl nitrite upon the cerebrum is very feeble, disturbances of intellection and of consciousness not being produced except by very decided toxic doses, and not being prominent symptoms of the poisoning. As was shown by H. C. Wood,[2] the lessening of reflex activity and of voluntary motion which undoubtedly occurs in toxæmia from the agent now under consideration is chiefly spinal in its origin, since after death the nerves and muscles preserve, though in an impaired condition, their functional power. On the motor centres of the cord the nitrite acts as a direct and powerful depressant, at the same time that it exerts a similar but much less pronounced influence on the nerves and muscles, decreasing, but not destroying, their functional life. The diminution of reflex activity is never preceded by a stage of functional excitement. In some animals convulsions do occur, especially when the drug is administered by inhalation ; but they are in all probability cerebral, not spinal, and due to the asphyxiating influence of the poison. Over the sensory nerves and centres amyl nitrite has but little power. They are among the last portions of the body to be affected, sensation being intact until near death : so that the drug is in no sense an anæsthetic.

Respiration.—It is certain that the respiratory centres are greatly depressed by full doses of amyl nitrite, the breathing becoming both slow and shallow, and death finally occurring from centric paralytic asphyxia. Mayer and Friedrich assert that small doses of amyl nitrite increase the rapidity and depth of respiration by stimulating the respiratory centres ; but this remains at present doubtful, it being probable that the increased respiration is secondary to the disturbance of the circulation, as is asserted by Winkler.

Circulation.—Although the pulse may be much increased in frequency sometimes from the very beginning by amyl nitrite, the arterial pressure is diminished, and finally is reduced almost to zero, the fall of pressure occurring equally after section of the vagi as at other times. As the num-

ber of heart-beats in the uninjured animal is increased rather than diminished, while the strength of the individual beat is not perceptibly lessened, it is evident that, at least in the early stages of the poisoning, the diminution of arterial tension is not cardiac in origin, but must be due to dilatation of the capillaries. This conclusion is confirmed by an experiment of Brunton, who found that if the descending aorta were tied high up, no perceptible fall of pressure was produced by the inhalation of the amyl salt until very late in the poisoning, when the heart itself was acted upon by the drug ; also by the fact noted by Amez-Droz [3] and by Gaspy,[4] that the vessels of the rabbit's ear and of the frog's web can be seen to dilate when the salt is inhaled.* In man the flushing of the face and of the retina, as noted by Charles Aldridge,[5] indicates that the nitrite acts locally, probably upon some centre, before it does generally, as general dilatation of the vessels causes pallor.

An interesting question which here arises is, whether the dilatation is centric, due to an action on the vaso-motor nerve-centres, or peripheral, due to a direct action on the muscular coat of the arterioles. We believe that it must be peripheral, and not centric, in its origin, since both in our own experiments and in those of Brunton it occurred after the arterioles had been separated from the vaso-motor centres by division of the cord. This fact appears to prove that the fall of arterial pressure is due to a direct paralyzing action of the drug upon the coats of the arterioles,—a conclusion confirmed by our knowledge of the local action of the nitrite upon muscular tissue.

Bernheim, however, asserts that this cannot be so, and that the dilatation must be solely due to an action upon the vaso-motor centres, because he found that galvanization of the cervical sympathetic still caused contractions in the vessels of the ear of a rabbit to which amyl nitrite had been given. As pointed out by Pick,[6] Bernheim's experiment does not warrant his conclusion. It only shows that the muscle-fibres in the walls of the vessels are not so completely paralyzed as to be unable to respond to very powerful stimuli. W. Filehne [7] also dissents from the view that the action of the nitrite is upon the vessels. It is very probable from the general sedative effect of the drug upon the motor centres that it acts also upon the vaso-motor centres ; and when the local flushings caused by small doses of the poison are borne in mind, this probability is greatly enhanced. Filehne affirms that when to animals, whose lungs are exposed, inhalations of the nitrite were given, the change of color was not nearly so great as in the ears, and that if the sympathetic had been destroyed in the neck of a rabbit, and amyl nitrite exhibited, the vessels on the unwounded side actually became larger than those of the opposite ear. The answer to these results is, that opening the chest must derange most profoundly the pneumonic circulation, and that all observations upon the comparative size of vessels are very apt to be mere guess-work when the change is slight. Moreover,

* A noteworthy fact asserted by Amez-Droz is that after a long period of dilatation the vessels contract again, whether the inhalation be continued or not. We think the explanation of this is simply that, owing to the volatility of the nitrite, it soon all escapes from the dossil of lint on which it is placed for inhalation ; an explanation strongly confirmed by a statement of Amez-Droz, that in these cases a new inhalation was followed by dilatation as before. Amez-Droz says only the arterioles dilate, but Gaspy found that both arterioles and veins were affected.

in Schuller's[8] experiments, after destruction of the cervical sympathetic in a rabbit, inhalations of the nitrite produced still further dilatation of the vessels of the ear.

Atkinson[9] and D. J. Leech[10] have each found that the nitrite enormously increases the flow of blood-serum which is being forced by a steady pressure through the decapitated tortoise, or through a recently excised kidney; a solution 1 in 10,000 had a distinct effect in widening the blood-paths. In conclusion, it seems to us established that amyl nitrite does act locally on the coats of the arterioles, although it may at the same time influence the vaso-motor centres.

In man the pulse-rate is enormously increased by amyl nitrite. In animals the amount of the increase varies, but in the higher groups the rule appears to be increase of the pulse-rate, which is especially decided in the dog. Filehne has by a single very ingenious experiment apparently shown that the acceleration is due to a depressing influence upon the inhibitory centres. He divided the par vagum in a rabbit, employed an electric current to the severed nerves of sufficient strength to bring the pulse-rate to normal, and found that the amyl salt was powerless to affect the rapidity of the cardiac action. Certain experiments performed by Mayer and Friedrich[11] confirm that of Filehne. It is known that sudden asphyxia slows the pulse by exciting the inhibitory centre. Mayer and Friedrich found that this action is prevented by the inhalation of the amyl salt. Then, again, they found that when by compression of the arteries the blood was prevented from going to the head, the nitrite did not increase the rapidity of the pulse, and also determined that the reflex inhibitory slowing of the heart by irritation of a sensitive nerve is prevented by amyl nitrite. Further, in dogs with a powerful cardiac inhibitory apparatus the primary influence of the nitrite is more marked than it is in rabbits, whose pneumogastrics are very feeble. The sudden, thumping action of the heart which is so prominent in man when the nitrite is inhaled is therefore probably, at least in part, due to depression of the inhibitory apparatus. There is, however, as pointed out by Reichert,[12] some reason for believing that in small doses the nitrite acts primarily as a stimulant to the heart. Lauder Brunton long ago discovered that if the aorta be compressed so as to eliminate in great part the influence of the vaso-motor system, the nitrite causes a primary rise in the arterial pressure; and it is perfectly possible for an excessive heart-action to be more than neutralized, so far as the arterial pressure is concerned, by a vaso-motor depression, so that the immediate fall of pressure caused in the normal animal by the nitrite is not proof that the heart may not be stimulated. In G. A. Atkinson's experiments, 1 part of the nitrite in 20,000 produced a slight increase in the working power of the cut-out frog's heart (Williams's apparatus); 1 in 10,000 caused a rise for four or five minutes, followed by a fall; smaller and larger amounts than these had either no effect or lessened the heart's action.* It seems, therefore, that

* There is, however, still much uncertainty about the matter. D. J. Leech affirms that 1 in 10,000 always quickens and weakens the beat of the isolated frog's heart in a

our present physiological evidence justifies the belief that very small quantities of amyl nitrite primarily stimulate the heart, although it is demonstrated that in moderate or large amounts the drug respectively depresses or paralyzes the heart-muscle.

Urine.—F. A. Hoffmann[14] found that in the rabbit a hypodermic injection of 0.111 to 0.113 gramme of the drug is enough to cause diabetes. If twice this amount of the amyl salt is used, the sugar becomes very abundant in the urine, and continues to be present for from twelve to thirty hours. Consentaneously with the elimination of sugar there is a great increase in the amount of the urine. The occurrence of glycosuria in man has not been recorded ; it is produced by toxic doses only, if at all.

Temperature.—Amyl nitrite, in whatever way exhibited, if given in sufficient amount, reduces most remarkably animal temperature. We have seen a pigeon perfectly conscious although its temperature had been brought down by this agent some 13° F. This influence is as marked in fever as in the normal condition of the animal, and is independent of the nerve-centres, occurring after section of the cord, and even after death in those cases in which post-mortem rise or continuance of high temperature normally takes place. We have also experimentally determined that it is associated with diminished excretion of carbonic acid. It must therefore be due to a direct arrest or check of tissue-changes or oxidation within, or without, the blood. The mouth-temperature in man is certainly sometimes elevated by the inhalation of amyl nitrite, but the rise is a very temporary one. W. A. Manassein and N. Sassezki[15] found, in a number of studies upon normal and fevered men, that while the peripheral temperature was at first increased the rectal temperature was always reduced, and after a time the surface of the body grew cooler. The maximum reduction was reached in one to one and a half hours, and in a case of fever amounted to 3° C.

The vapors of the nitrite have a very marked influence over oxidation outside of the body, as is shown by many facts, of which it is only necessary here to cite the extinguishment of glowing phosphorus by a few drops of the amyl salt diffused through the jar. It cannot be doubted that within the economy the same thing occurs. If, however, the arrest of oxidation were complete, instant death from suffocation would result. The true explanation of the symptoms evidently lies in diminution, not destruction, of oxidation.

When an animal inhales amyl nitrite, the arterial and venous blood soon become of a nearly uniform hue, which resembles somewhat that of normal venous blood, but is quite distinct from it, having a chocolate tint. Moreover, this chocolate-colored blood does not assume the arterial hue when shaken with the air.

Roy apparatus. In a single experiment made with amyl nitrite on the isolated mammalian heart, Bock[13] came to the conclusion that the amyl nitrite has no effect upon the heart itself. The experiment, however, does not seem to us sufficient, and the method employed is open to very grave objection.

Arthur Gamgee [16] discovered that as the chocolate color is assumed by the blood the two spectrum bands of the oxyhæmoglobin disappear and are replaced by new bands, nearly, but not exactly, in the place of those of acid hæmatin. If ammonia be added to the chocolate blood, the color changes back to a blood-red again, and simultaneously the spectrum lines regain their normal position. If a reducing agent, such as ammonium sulphide, be added to the chocolate blood, it is able to deoxidize the oxyhæmoglobin, but, before doing so, evidently removes it from union with the nitrite, since the new bands disappear and those of oxyhæmoglobin reappear in the spectrum before the lines of the reduced hæmoglobin manifest themselves. Gamgee also found that the amyl nitrite blood had lost its power of absorbing oxygen, or of yielding oxygen to the air-pump, and that carbonic oxide gas added to the blood did not expel oxygen from it. Having thus determined that a new compound is formed in the blood by the nitrite, Gamgee finally succeeded in obtaining it in a crystalline form. As he always upon analysis found the nitrite in this compound, he considered it to be a nitrite-oxyhæmoglobin.

Recent researches have demonstrated that the spectrum of this new compound is identical with that of the *methæmoglobin* of Hoppe-Seyler,[17] so that the identity of the two substances is very probable.

These facts do not seem to us to prove that amyl nitrite entering into the blood-vessels at once overpowers the hæmoglobin of the blood-corpuscles and checks all oxidation. As already stated, the experiments of Gamgee showed conclusively that this new compound yields its oxygen to reducing agents. Further, Gamgee found that when the nitrite blood was brought into contact with prepared guaiacum-paper it still ozonized it, though not so actively as normal. It is evident that the blood-corpuscles retain to a greater or less degree their power of yielding ozone to bodies desiring it, and are capable of exerting at least this portion of their respiratory function : further, when this ozone is given up and the oxyhæmoglobin changed into hæmoglobin, so far as our present knowledge goes, the hæmoglobin must absorb more oxygen before it can reunite with the nitrite. Evidently, then, absorption of oxygen must take place ; evidently the blood-corpuscles must perform their respiratory function ; but evidently also they are greatly crippled and impaired in the rapidity and ease of its performance. Hæmic respiration is, in other words, greatly interfered with, but not abolished.

The accord of the results of this chemical investigation with those arrived at by a purely physiological study of the drug is very striking and very beautiful, both teaching the same thing,—lessened but not absolutely arrested oxidation.

Having ascertained the existence of diminished oxidation in poisoning by amyl nitrite, the temptation is very strong to attribute all the symptoms produced by it to this arrest. We think, however, that without reasonable doubt amyl nitrite directly affects the nerve-centres for the reasons given below.

In the first place, potassium nitrate and other nitrates, according to Gamgee, act in the same manner upon the blood, yet the symptoms caused by them are very different from those caused by amyl nitrite. In the second place, when arrest of

oxidation is caused by deprivation of oxygen, as during the inhalation of pure nitrogen, the symptoms are very different, the brain and consciousness being always affected before the centres of reflex action, whereas under the influence of amyl nitrite the contrary occurs. In the third place, other substances, such as toxic doses of alcohol, check oxidation, but do not cause the same symptoms as does the drug under consideration.

In sufficient dose amyl nitrite is poisonous to the white corpuscles; Atkinson has found that 1 in 1000 kills the corpuscles in fifteen to twenty minutes.

SUMMARY.—The dominant physiological action of amyl nitrite is upon the spinal cord and the circulation. Under its influence arterial pressure falls from paralysis of the blood-vessels, chiefly as the result of a direct action upon the muscles in their walls. At the same time the peripheral vagi are paralyzed and the heart is stimulated directly or indirectly, the number and force of its contractions being increased, this period of stimulation after moderate doses gradually subsiding into the normal state, but after toxic doses passing into one of cardiac paralysis, with a final arrest in diastole, which is due to a direct action upon the heart-muscle or contained ganglia. Paralysis of motion and loss of reflex activity, prominent phenomena of advanced poisoning, are due to a direct action upon the motor side of the spinal cord. Death results finally from paralysis of the respiratory centres. By a direct action upon the red blood-corpuscles the hæmoglobin is converted into a new compound, probably methæmoglobin. The fall of the bodily temperature is probably the result of lessened oxidation. Locally applied in concentrated form, amyl nitrite paralyzes all higher tissues.

THERAPEUTICS.—Amyl nitrite is employed to meet indications which are very closely in accord with its known physiological action. It should be remembered, however, that its influence is all over in from ten to twenty minutes after its ingestion, and it is therefore a remedy useful only in cases of crises or fugacious conditions. It may be employed in all cases in which it is desired to dilate the capillaries. During the algid stage of an ordinary *intermittent fever* it will put an end immediately to the chill, but does not affect the development of the hot stage. It might possibly be of service in the algid stage of a *pernicious malarial fever*.

Led by the evidences of arterial spasm in the sphygmographic tracings in a case of *angina pectoris*, Lauder Brunton in 1867 suggested its use in that disease. As the pathology of these cases of heart-pang is not definitely made out, it seems useless to speculate how the nitrite acts in many cases; but there is abundant evidence of its value in relieving almost instantly agony which has resisted all other treatment. This appears also true whether valvular disease or merely functional disorder exists. Foster[18] has found the drug of great service in aortic insufficiency with excessive hypertrophy and severe frontal headache.

The violent cardiac action which is produced by the inhalation of the nitrite has led to its employment as a cardiac stimulant, and it has been much commended by various clinicians in all forms of sudden *heart-*

failure, even when such failure is dependent upon fatty degeneration or other disease of the heart itself. The direct stimulant influence, if it exist at all, of amyl nitrite upon the heart is, however, of the briefest duration, and if the least overdose of the drug be given, passes into cardiac depression. The zone between stimulation and depression of the heart by the nitrite is so narrow that the greatest care must be exercised whenever there is any cardiac disease, or whenever the heart is violently depressed by such a poison as chloroform. Although Reichert states that he has seen the blood-pressure and pulse-wave, which had been depressed almost to zero by ethylene bichloride, greatly increased by amyl nitrite, in an elaborate series of experiments made by H. C. Wood with chloroform no such effect could be obtained, and in recorded cases of cardiac failure in anæsthesia the amyl salt has failed. Its use should always be tentative.

Its physiological action would indicate that it should be of service in all cases of spasm of the capillaries, of the bronchial tubes, and of the muscular system generally. Accordingly, Oscar Berger [19] and others have used it with very good effect in *migraine* with capillary contraction.

Amyl nitrite is of very great value for the purpose of relaxing spasms; it will usually abort a paroxysm of *asthma*, but in practice it will be found that the asthmatic patient becomes so rapidly accustomed to the use of the drug as to make it of comparatively little value. In a fully formed paroxysm of *epilepsy* it must be used with caution, because the patient's condition will obscure its early effects ; but in the *status epilepticus*, when there is an almost indefinite repetition of the fits, the remedy may be of great use in stopping the convulsions. When there is a notable interval in ordinary epilepsy between the aura and the convulsion, the latter can usually, if not always, be entirely prevented : the patient should carry a small vial containing a few drops of the drug or so-called "pearls" (minute flasks, each containing five minims, which are to be broken in a handkerchief), and should inhale the amyl salt so soon as the aura is felt.

S. Weir Mitchell [20] calls attention to the value of the nitrite as an aid in diagnosing those occasional cases of nervous disorder in which *petit mal* is simulated by attacks really due to passing congestion of the nerve-centres. He asserts that in these cases amyl nitrite instead of arresting the paroxysm increases its severity.

In nervous *spasmodic dysmenorrhœa*, it is stated by various authorities that inhalation of amyl nitrite will sometimes bring immediate relief, two to six drops being given when the pain comes on, and repeated *pro re nata*. As was first pointed out by William F. Jenks,[21] the nitrite is most effective in arresting *puerperal convulsions*, but if the convulsions occur shortly after parturition the use of the nitrite is attended by the greatest danger of producing uterine relaxation and serious or even fatal post-partum hemorrhage.

Amyl nitrite is a very valuable remedy in the treatment of *tetanus* and of *strychnine-poisoning*. In the experiments of St. Clair Gray,[22] which have been substantially confirmed by Hobart A. Hare,[23] although one-

quarter of a grain of strychnine was found to be sufficient to cause death in an immediate convulsion in the rabbit, no decided symptoms whatever were induced in two rabbits by the subcutaneous injection into each of half a grain of strychnine with ten drops of the nitrite. During a paroxysm of cramp asphyxia from strychnine, the poison of tetanus, or other similarly acting cause, the nitrite should be given hypodermically, the lack of respiratory movement interfering with its absorption through the lungs.

TOXICOLOGY.—We know of no deaths recorded from amyl nitrite, though very alarming symptoms have resulted in various cases. Ten minims of a ten per cent. solution, hypodermically injected, are said to have been followed by two successive furious epileptic convulsions, each preceded by arrest of respiration and of the heart's action, to which arrest they were probably due.* Three drachms caused no other symptoms than violent vomiting. One drachm occasioned great weakness, cyanosis, and very feeble, slow, intermittent pulse. Two drachms caused vomiting within five minutes, great weakness of the pulse, slow respiration, temperature below 95° F., semi-coma, with hæmoglobin, but no sugar or blood-corpuscles, in the urine for twelve hours after the poisoning.

The best treatment for the poisoning would consist in favoring vomiting by apomorphine or other agents, and the use of artificial respiration and hypodermic injections of strychnine and digitalis. That there is between the latter drug and a nitrite, so far as the circulation is concerned, direct antagonism has been shown by C. R. Marshall,[24] who found that, in accordance with the doses used, the vaso-dilator influence of the nitrite would put an end to the high pressure caused by digitalis, or that digitalis would elevate the lower blood-pressure of the nitrites, or that the two drugs would just counteract each other, and that digitalin would overcome the diastolic cardiac arrest produced by the nitrite, or the nitrite, if in excess, would overcome the systolic arrest of the frog's heart produced by digitalin.

ADMINISTRATION.—As already stated, the method of administration usually employed hitherto is inhalation, from one to three or five drops being placed on a handkerchief and held near the mouth or nose, the handkerchief being removed so soon as a sense of fulness of the head is experienced. We have given it by the mouth, dropped upon a lump of sugar and taken instantly in doses of two or three drops. There is not at present sufficient evidence to enable us to decide as to the maximum amount of the drug which it is safe to give. In a case of cholera, D. B. Smith[25] exhibited hypodermically two drachms in the course of an hour and thirty-six minutes without inducing any serious symptoms, and a dose of a dessertspoonful has been recovered from,[26] emetics being given. Used with care, the nitrite, although a very rapidly acting and

* Strahan (*Journ. Ment. Sci.*, xxx. 252), J. Roesen (*Centralb. f. Klin. Med.*, 1888), George E. Shoemaker (*Med. News*, 1893, i.), and Stansfield (*Brit. Med. Journ.*).

powerful agent, seems to be safe, since we have never seen either in man or in the lower animals any sudden or unexpected action,—any influence out of proportion to the amount given. It must be borne in mind that the symptoms generally increase in intensity for a minute or two after the withdrawal of the drug from inhalation.

ETHYL NITRITE.—It is not to be doubted that all of the nitrites depend for their physiological activity on their acid-radical, and that most of them have similar physiological properties. This has been shown to be true of ethyl nitrite (Richardson[1] and Leech[2]). Leech asserts that the ethyl nitrite has the great advantage over the amyl salt of greater permanency of action, the effect of the single dose lasting from a half to two hours. He highly commends in *asthmatic bronchitis* a solution, which he states to be stable, composed of three parts of ethyl nitrite, five of glycerin, and ninety-two of absolute alcohol; dose, thirty to ninety minims (2–6 C.c.).

POTASSIUM NITRITE.—It has been demonstrated by E. T. Reichert[1] that the general physiological action of sodium and of potassium nitrite is indistinguishable from that of amyl nitrite, except in being much less rapid and more permanent. (See also G. A. Atkinson.[2]) Doses of six to ten grains in man sufficed to raise the pulse to 110 or 120, with flushing of the face and intra-cranial throbbing; the symptoms usually began in twenty minutes and lasted several hours, and were in no case disagreeably severe. Eructations of a phosphorus-like taste were nearly always present. Ten to fifteen grains have produced complete muscular relaxation, livid lips, headache, etc., lasting three hours. Twenty grains of the commercial sodium nitrite have been given without serious effect, but of a pure article, either of the sodium or the potassium nitrite, the dose is three grains (0.2 Gm.); five grains have produced serious symptoms.[3] The dose may be repeated every two hours cautiously.

SPIRITUS GLONOINI. U. S.—*Spirit of Glonoin* is a one per cent. alcoholic solution of *glonoin trinitrate* or *nitroglycerin*. It is a clear, colorless liquid, having the odor and taste of alcohol. As very minute quantities are capable of producing violent symptoms, great care should be exercised in tasting it or in applying it to the skin. Moreover, if any considerable quantity of it be spilled, the evaporation of the alcohol is liable to be followed by a dangerous explosion. Full therapeutic doses of the spirit of glonoin cause in man giddiness, constriction, or other abnormal sensations in the head, often amounting to severe headache, choking in the throat, sometimes nausea, and rapid cardiac action, with lessened arterial pressure. After toxic doses there is great failure of the heart's action. A single drop is said to have caused insensibility, and in the case of Mr. Field,[1] who took two drops, loss of consciousness and of the pulse at the wrist was complete. J. Noer[2] attributed the follow-

ing symptoms in a woman to the use of ten-drop doses of the alcoholic solution of nitroglycerin. The pulse was slow, intermittent, and very irregular, the pupils dilated, the urine scanty and containing considerable pigment. There were also pain in the region of the heart, intense headache, sense of constriction around the forehead, and great weakness of the muscles. Lauder Brunton and Tait[3] have found that upon blood-coloration, arterial pressure, nerve-centres, and muscles nitroglycerin acts very much as does amyl nitrite. This similarity of action between nitroglycerin and the nitrites has been confirmed by Murrell and Matthew Hay,[4] also by A. Henocque,[5] and is remarkable, as nitroglycerin may be regarded as glyceryl nitrate. It has been shown, however, by Hay, that during its alkaline decomposition it yields nascent nitrous acid, and it can scarcely be questioned that this acid is developed in the blood and acts upon the system.

The effect of nitroglycerin is certainly more prolonged than is that of amyl nitrite. The statement of Korczynski,[6] that the maximum effect of a dose in man is reached in from three to five minutes, whilst the influence is dispersed in three-quarters of an hour, is as accurate as can be made. Nitroglycerin has come into great favor for all conditions in which amyl nitrite has been employed. In *angina pectoris*, in *cardiac failure*, in *asthma*, in *uræmia*, and in *puerperal eclampsia* it may be substituted for amyl nitrite with advantage whenever any persistency of action is desired. It is also very largely used in cases of habitual high arterial pressure, especially in *arterial fibrosis* in which the increased peripheral resistance is developing or has produced increased cardiac power. Even its action is, however, too fugacious to be of much service in these cases, and it should be administered every hour when a decisive effect is wanted. In some cases of *acute apoplexy* with high arterial pressure it might be of great service. The dose is one to two minims (0.06–0.12 C.c.).

LOBELIA. U.S.

The leaves and tops of the indigenous herb Lobelia inflata. The dried plant has a slight irritating odor and a taste at first scarcely perceptible, afterwards burning, acrid, and attended by a flow of saliva. Proctor discovered the alkaloid *lobeline*, which was long believed to be liquid, until J. U. and G. G. Lloyd obtained it in broad, colorless, odorless, and tasteless crystals.*

Physiological Action.—The symptoms produced by large doses of lobelia in man are nausea, soon followed by violent vomiting, accompanied by intense prostration, as is shown by feeble pulse, cold sweats, pale skin, and great muscular relaxation. Purging may or may not occur. Numerous cases of fatal poisoning by it have been recorded. The symptoms are those above mentioned, intensified; in some cases

* The Messrs. Lloyd also assert that there is a second alkaloid in lobelia, but the researches of Dreser[1] render it probable that this second alkaloid is a derivative from lobeline.

vomiting does not occur, and it is especially under these circumstances that fatal effects have been noted. Burning in the fauces and œsophagus, and epigastric distress, in addition to the intense prostration, bordering upon collapse and finally merging into complete collapse, with coma, stupor, muscular tremblings, and in some cases convulsions, precede the fatal termination.

In mammals the symptoms produced by lobelia are : slowing and irregularity of the respiration ; progressive failure of the muscular power ; violent vomiting in those animals which have the power of vomiting ; dilated, fixed pupil ; convulsive seizures ; fall of the bodily temperature, and death from asphyxia, the heart continuing to beat after the failure of respiration, the dominant physiological action of the drug being its influence upon the respiratory centres. When given to the frog, lobeline produced failure of voluntary movement, with distinct loss of coördination and disturbances of respiration. Unless the dose has been too large, there is primary increase of the reflex activity, which, however, sinks below the normal until it is lost.

All experimenters seem to be in accord in concluding that the final paralysis caused by lobelia is due to a direct *paralyzing action upon the motor nerves.* Berstein called attention to the fact that the spinal cord of the frog is usually supplied with blood from the anterior spinal artery, and that by thorough and complete section of the cord the lower segment is cut off from the general circulation. Experimenting in accordance with this, Dreser[1] found that the increased reflex activity produced by lobelia was confined to the anterior section of the cord and tributary muscles, and concludes that lobeline is a direct spinal stimulant.

Respiration.—The researches of Dreser seem to show that both the respiratory centre and the vomiting centre in the medulla oblongata are primarily excited by lobeline ; hence the vomiting, and hence, also, the increase not only in the rate of the respiration, but in the amount of air taken in and out from the lungs, as observed by Dreser. This condition of excitement is followed by paralysis of the respiration, which after very large doses may come on abruptly, even within two or three minutes after the injection of the poison. According to Dreser, the paralysis of the motor nerves, noted in the frog, is of little importance in the mammal, the respiratory centre being so susceptible to the drug that it is paralyzed before the nerves. Dreser also found that there is a peripheral palsy of those vagus filaments which have influence upon the bronchial muscles.

Circulation.—According to Ott[2] and Afanasieff,[3] lobelia produces a rise of the arterial pressure, which in Ott's experiments was not prevented by previous high-up section of the spinal cord, and must, therefore, be due to an action either of the heart or of the muscles in the arterial walls. Because he found that no rise of pressure is produced by lobelia in the nicotinized rabbit, Ott concludes that the alkaloid is a stimulant to the arterial walls. On the other hand, in the experiments of Afanasieff, lobeline caused in the frog's heart a period of increased work, followed, if the dose were large enough, by loss of power ending in diastolic arrest.

In the later stages of lobeline-poisoning the arterial pressure falls progressively, so that it is probable that lobelia first stimulates and afterwards paralyzes both the heart and the arteries. A very important point to be noted is that the action of lobelia upon the circulation is entirely subordinate to its influence upon the nerve-centres, especially upon respiration, and is, therefore, of no value to the therapeutist.

TOXICOLOGY.—The symptoms of lobelia-poisoning have been sufficiently described. The treatment should consist in washing out the stomach with plenteous draughts of a warm solution of tannic acid, in the free exhibition of opium, alcohol, ammonia, strychnine, and digitalis, and in the use of external stimulation by dry heat, frictions, mustard, etc., precisely as in poisoning from veratrum viride.

THERAPEUTICS.—The former use of lobelia as an emetic, and for the purpose of relaxing spasm in various diseases, has been entirely superseded by more effective and less dangerous remedies. Lobelia remains, however, a valuable drug in the treatment of *asthma*, or acute *bronchitis* with *bronchial spasm*, in which it may be given in small repeated doses at long intervals, or in severe attacks every few minutes until nausea is induced. An infusion (one ounce to a pint) has been strongly recommended as a local application in the *eczema* produced by the *Rhus toxicodendron*, or "*poison-vine*." The dose of the tincture (TINCTURA LOBELIÆ—twenty per cent., U. S.), as an expectorant, is ten to twenty minims (0.6–1.2 C.c.); in the paroxysm of asthma, one-half to one fluidrachm (2–4 C.c.) every half-hour until nausea is induced. That of the fluid extract (EXTRACTUM LOBELIÆ FLUIDUM, U. S.) is, as an expectorant, one to five minims. According to S. Nunes,[4] from five to forty centigrammes of lobeline may be given a day, but in any case the first dose should not exceed one-fortieth of a grain, to be increased *pro re nata*.

GELSEMIUM. U. S.

The root of Gelsemium sempervirens, the *yellow* or *Carolina jessamine*, a beautiful climbing plant of the Atlantic Southern United States, distinguished by its large, axillary, very fragrant, clustered blossoms and perennial dark green leaves. The very light, fibrous, dirty yellowish root has a bitterish taste, and contains an alkaloid, *Gelsemine*, in combination with *Gelseminic Acid*, both discovered by Wormley.

PHYSIOLOGICAL ACTION.—*Absorption.*—The alkaloid gelsemium is rapidly absorbed and is eliminated unchanged by the kidneys.

General Action.—There is a wide range of susceptibility in man to the influence of gelsemium, some individuals being profoundly influenced by a dose which has no perceptible effect upon another person. After the smallest active dose (five to fifteen minims of the fluid extract), the only symptom is languor; with it may be a little lowering of the force and frequency of the pulse. When a somewhat larger amount is ingested, to the languor are added dizziness and disturbance of vision, with, in some cases, a pain over the brows. Ringer and Murrell[1] state that the pupil

is contracted, but this is probably an inconstant result. After toxic doses of the poison the muscular weakness is extreme, and in several cases[2] the flexors of the arms have been especially affected. The disturbance of sight is now very marked ; double vision, or partial or even complete blindness, may exist ; the pupil is widely dilated and immovable ; the external rectus muscle is weakened, sometimes sufficiently to produce a marked internal squint ; the eyelid droops, and is raised with difficulty or falls in paralytic ptosis. If the patient is able to walk at all, the gait is staggering ; the jaw drops, articulation fails ; the general sensibility is much impaired ; the respiration slow and labored ; the pulse feeble and thready ; the skin bathed in a cold sweat ; the bodily temperature greatly lowered. Sometimes drowsiness is felt after moderate doses of the poison, but consciousness may be preserved in the midst of very severe symptoms, although in all the fatal cases whose record we have met with it has been lost before death. The drug acts very promptly, symptoms usually appearing in about twenty minutes after its ingestion, and beginning to subside in two or three hours.

Gelsemium produces in the lower animals symptoms similar to those which it causes in man, with the exception that convulsions are very generally developed.

The convulsions are not always present, but they have been observed in the frog, pigeon, cat, rabbit, and dog. The loss of voluntary power precedes the convulsions, and in the careful experiments of Ringer and Murrell upon frogs it was found that the cord was rapidly exhausted by repeated irritations, so that convulsions could not at once be induced. Bartholow states that in the rabbit, cat, and pigeon the convulsive movements are backward, sometimes amounting to complete somersaults.

Nervous and Muscular Systems.—Cerebrum.—The retention of consciousness until very late in the poisoning, both in man and in the lower animals, shows that the drug has very little power over the higher cerebrum, although the drowsiness and the final loss of consciousness prove that it is not entirely devoid of such influence. The convulsions are not cerebral, as is proved by their occurrence in the pithed frog (Ringer and Murrell), and below the point of section in mammals with divided spinal cord (Taylor[3]).

Both the convulsions and the paralysis in poisoning by gelsemine are spinal. Their development is not affected by tying an artery before poisoning, so as to protect a limb (Bartholow,[4] Ringer and Murrell[5]) ; moreover, the afferent and motor nerves and muscles preserve their functional activity until death.* The convulsive stage of gelsemine-poisoning is preceded by exaggerated reflex activity (I. Ott[6]), so that gelsemine appears to cause spinal motor excitation followed by spinal motor paralysis.

The most plausible explanation of these phenomena is (in accordance with the doctrine of spinal inhibition, see page 172) that gelsemine is a depressant and,

* Ott, Bartholow, Ringer and Murrell. (For details, see eighth edition of this treatise.)

finally, paralyzant to both the spinal inhibitory ganglia-cells and to the spinal motor nerve-cells, but attacks primarily inhibition; so that in the first stage of its poisoning excessive motor activity results from the paralysis of spinal inhibition, whilst in the final stage there is a true motor paralysis due to a direct paralysis of the motor nerve-cells. Ringer and Murrell, however, conceive that there are in gelsemium two active, antagonistic substances, one a tetanizant,* the other a paralyzant; but in their own experiments, and in those of Ott, gelsemine believed to be pure produced convulsions. Ott, however, found gelsemic acid so much more powerful in its convulsive action than the alkaloid as to suggest the correctness of Ringer and Murrell's hypothesis.

Dr. Bartholow says that "it [gelsemium] acts also on the sensory portion of the cord, producing at last complete anæsthesia; but this effect in warm-blooded animals and in man is toxic only, and follows the paralysis of the motor functions." This may be correct, but, so far as we know, has not been experimentally proved.

Respiration.—Gelsemium usually kills by a paralysis of respiration. According to the researches of Burdon Sanderson and of Ringer and Murrell, immediately after the ingestion the extent of the respiration, but not its rate, is increased; very shortly, however, both rate and depth enter a condition of progressive palsy ending in death. The respiratory changes are the product of a direct action upon the respiratory centres, being uninfluenced by previous section of the vagi.

Circulation.—The action of moderate doses of gelsemium upon the circulation is not pronounced, but the toxic dose depresses both the pulse-rate and the pressure. As this occurs after previous section of all the cardiac nerves of the spinal cord (Ott[1]), it is probable that the poison exerts a direct influence upon the heart. How far or in what way it affects the arterial system we have no knowledge.

Eye.—Ringer and Murrell affirm that decided non-toxic doses of the drug cause contraction of the pupil. However this may be, marked dilatation of the pupil is a very constant symptom in the poisoning, and the local application of gelsemine to the eye produces violent mydriasis, with paralysis of accommodation.

It would seem probable that the mydriasis is due to an action upon the peripheral nerve-ending in the eye. The palsy of the external rectus and the ptosis indicate that such action is paralytic, so that it is a probable conclusion that peripheral oculo-motor paralysis is the cause of the dilatation of the pupil. The falling of the jaw and the loss of the power of articulation indicate that all the motor nerves of the head are acted upon by the poison.

SUMMARY.—The characteristic symptoms of gelsemium-poisoning are progressive muscular weakness, double vision, dilated pupils, squint,

* In confirmation of this, A. R. Cushny (*Arch. für Exper. Pathol.*, 1892, xxxi.) finds that there are two bases in gelsemium, to one of which he gives the name *gelsemin*, the other *gelseminin*. Gelsemin, he finds, produces in the frog violent spinal excitement with increase of the reflexes, followed by paralysis due to an action upon the nerve-endings. Gelseminin is the more active of the two, producing a paralysis by direct action upon the spinal centres and having also a curare-like paralytic influence upon the nerve-trunks.

ptosis, and dropping of the jaw. The chief physiological action of the remedy seems to be depression of the motor spinal cord, including the respiratory centres; the depression apparently being preceded by a stage of stimulation. The effect of the remedy upon the circulation is not pronounced, but toxic doses depress directly the heart and arterial pressure.

THERAPEUTICS.—Gelsemium was originally employed as an arterial sedative and febrifuge in the *malarial fevers* of the South, and subsequently in other *sthenic fevers*. It appears in some way to depress the bodily temperature, but certainly possesses no controlling influence over the arterial system at all comparable to that of veratrum viride and aconite. Bartholow commends it highly in *pneumonia* and *pleuritis;* its influence for good in these disorders would seem, however, to be chiefly associated with its power of lessening the rapidity of respiration and increasing the tendency to perspiration. It does not appear probable that any advantage to be derived from it will counterbalance the dangers attending its employment in the large doses required. In *asthma*, *spasmodic laryngitis*, *whooping-cough*, and *nervous cough*, in which it is also recommended by Bartholow, its employment seems more plausible, as in these cases there is a distinct spasmodic element. The testimony to its value in cases of *trigeminal*, *ovarian*, and other *neuralgias* is strong. How it does good in these disorders is as obscure as is the nature of the neuralgias, and in our hands it has usually failed. The marked effect of the drug upon the facial nerves would appear to indicate its employment in facial neuralgias, and especially in facial spasmodic affections. In acute *mania* the drug may be employed in full doses as a calmative.

TOXICOLOGY.—I. Ott has collected six cases of fatal poisoning, a teaspoonful of the fluid extract being the smallest amount that has caused death in the adult. Wormley believes that his chemical examinations have shown that in one fatal case the fluid extract ingested could not have contained more than one-sixth of a grain of the alkaloid.

The treatment of gelsemium-poisoning should be conducted on general principles. Our present knowledge does not indicate that morphine and gelsemium are physiological antagonists, but George S. Courtright[8] asserts that they have such relation, and details a case in which recovery occurred after the ingestion of from one to two teaspoonfuls of the tincture, one and one-half grains of morphine having been given hypodermically and one grain by the mouth.

ADMINISTRATION.—The dose of the fluid extract (EXTRACTUM GELSEMII FLUIDUM, U. S.) is five minims (0.3 C.c.) every two hours until constitutional effects are produced; of the tincture (TINCTURA GELSEMII —fifteen per cent., U. S.), ten to twenty minims (0.6–1.2 C.c.).

TABACUM. U. S.—Although *tobacco* is still recognized by the United States Pharmacopœia, it is not at present used in practical medicine, and we shall here discuss it very summarily, referring the reader to the tenth edition of this treatise for an elaborate study of its physiological action.

Tobacco depends for its activity upon the presence of an alkaloid, *nicotine*, a poison of such intensity that it has caused death in three minutes. The fatal dose of nicotine has not been made out. One-thirty-second of a grain will cause serious symptoms; one-seventh of a grain has been recovered from. The symptoms produced by tobacco in those unaccustomed to its use are horrible nausea and vomiting, giddiness, intense malaise, with weakness, followed, if the dose has been sufficient, by burning pain in the stomach, purging, free urination, extreme giddiness passing into delirium, a rapid, running, and finally imperceptible pulse, cramps in the limbs, absolute loss of muscular strength, a cold, clammy skin, and finally complete collapse, terminating in death.

In the lower animals, especially in the frog, to the symptoms commonly seen in man are added violent convulsions, which are of spinal origin and are followed after a time by paresis, which is probably also in part of spinal origin, although it has been demonstrated that tobacco is a powerful *depressant to the motor or efferent nerves*, acting primarily upon their peripheral filaments. The afferent or sensory nerves are much less affected than the motor, but are probably also depressed. The sympathetic ganglia are first stimulated and then depressed by nicotine. To these actions are probably due the increase of saliva and other secretions caused by small doses and the lessening of gland activity produced by large doses. Upon the voluntary muscles the drug has no action.

Upon the circulation nicotine has a very distinct influence, producing first rise and afterwards fall of pressure. The rise of pressure is certainly in part due to stimulation of the cardiac muscles or ganglia, but probably is also in part the outcome of peripheral contraction of the vessels; and it is further probable that the final paralysis is due to a double depressing influence upon the heart and the arterial walls, although these points have not been distinctly proved.

Upon the pupil nicotine acts as a myotic, probably paralyzing the peripheral ends of the sympathetic, and almost certainly stimulating the oculo-motor nerves.

The only use now made of tobacco in medicine is in the preparation of ointments for painful *hemorrhoids*, and in the form of a strong wash for *pruritus*. Its free external use is always accompanied by danger, and has caused death.

The dose of tobacco is five grains (0.32 Gm.), in infusion.

Toxicology.—A large number of deaths have resulted from the medicinal use of tobacco, Husemann[1] stating that no less than ten fatal cases have been caused by tobacco enemata alone. Copland[2] has seen a clyster containing half a drachm produce death. Even smoking has caused an acute fatal poisoning. Melsens affirms that the smoke of half an ounce of strong tobacco contains sufficient nicotine to prove fatal.*

* For a number of cases, see Stillé's *Therapeutics*, ii. 374.

In the only case of criminal nicotine-poisoning on record, an unknown amount of the alkaloid was forced into the mouth of the victim, causing death in from three to five minutes.[3] The treatment of tobacco-poisoning consists in washing out the stomach, the free administration of ammonia and alcohol, the hypodermic use of moderate amounts of strychnine, and the employment of such external measures as dry heat, rubbings, etc. If these fail, artificial respiration should be maintained. The excessive use of tobacco produces in some persons serious nervous disturbance, such as insomnia, irritability, general feebleness ; the most characteristic symptom is a peculiar irregularity of the heart's action, often accompanied by distinct intermissions. Amaurosis is also sometimes present.* Jonathan Hutchinson[4] affirms that he has seen this amaurosis recovered from by the use of opium and champagne without the abandonment of the habit of smoking. We have seen impotence as the only distinct symptom of chronic tobacco-poisoning.

CONIUM. U.S.

The U. S. Pharmacopœia recognizes only the full-grown fruit, gathered while green, of Conium maculatum. The plant is umbelliferous, a native of Europe, but naturalized in the United States. The dried leaves have a strong heavy odor, increased by the addition of an alkali, and resembling somewhat that of mice. They are bi- or tripinnate, and very much incised. The fruits are one to two lines long, roundish-ovate, striated, with five crenated ribs on the outer sides of the easily separable halves ; the odor is that of the leaves. The active principle is *Conine*, a yellowish, oily, liquid alkaloid, highly volatile, of a strong odor similar to that of the urine of mice, and of a very acrid taste. It is freely soluble in alcohol and in ether, and slightly so in water, with which it forms a hydrate, and it coagulates albumin ; when exposed to the air it undergoes decomposition, becoming first brown, afterwards resinous ; heat accelerates the change.

Physiological Action.—*Local Action.*—Upon the mucous membranes conium acts as an intense irritant. In a concentrated form it is probably fatal to all highly organized tissues, Christison having proved this to be true in regard to the muscles which are not influenced by the alkaloid taken internally. It is absorbed with great rapidity, and escapes through the system chiefly if not solely through the kidneys. Zaleski and Dragendorff have found it abundant in the urine during the first twelve hours of the poisoning ; Prevost has seen the urine of poisoned ani-

* The diagnosis of tobacco amblyopia depends upon the history of the abuse of the drug, the failure to improve with optical therapeutics, and the presence of a scotoma, usually oval in shape and negative in character, particularly pronounced for red and green, while the periphery of the field of vision remains unaltered. If, in addition, there is a quadrant-shaped patch of atrophic pallor in the nerve-head, the diagnosis becomes still more certain. Atrophy of the nerve may result, but in many cases there is no structural change, as the symptoms may go off in a few hours (De Schweinitz's *Toxic Amblyopia*).

mals cause in a frog the characteristic general palsy, and in a doubtful case of poisoning this physiological test might decide the diagnosis.

General Action.—Full physiological doses of conium produce in man quietude, languor, and muscular weakness. After toxic doses the weakness becomes extreme, forcing the patient to the horizontal position, or causing him to stagger or fall from weakness of the legs when he attempts to walk. This weakness has in some cases been attended by burning in the mouth, fauces, or stomach, nausea, vomiting, and with a sense of pressure or even with severe frontal pain. As the case progresses consciousness is preserved, but the paralytic symptoms become everywhere pronounced. The pupils sooner or later dilate ;* amblyopia from paralysis of accommodation, diplopia from irregular weakness of the ocular muscles, and ptosis are almost universally present, and the voice may be weakened to a whisper or lost. Sensibility is maintained to the end. Free salivation or free sweating sometimes occurs.

The circulatory phenomena are very subordinate ; though the pulse-rate may at first fall, later it becomes more rapid. Consciousness is usually preserved until the last, but may be lost in asphyxial coma some minutes before death, which results from paralysis of respiration.

We have met with accounts of but four fatal cases of such character. In one, that of the mistress of Dr. Hermann Jahn, killed in a few minutes by from ten to fifteen drops of the alkaloid (quoted by Husemann), violent palpitation of the heart is said to have been a prominent symptom. The chief symptom in the second case[2] was universal paralysis, with total failure of voluntary movement and of the voice before consciousness was lost. Convulsive movements were present very late in the case. Sensation appeared not to be lost until death was at hand.

The third case[3] was that of a medical electrician, suffering from blepharo-facial spasm, who took, beginning four hours after the last of a previous series of divided doses of a fluid extract amounting to one hundred and eighty drops, at 4.10, 4.40, and 5.15 P.M. fifty minims (one hundred and fifty in all) of "Squibb's fluid extract." The first dose produced dizziness and muscular relaxation ; the second, great muscular weakness, inability to stand, and thickening of speech, without relief of the spasm ; the third, immediately, some nausea, and tremors about the chest. At 6.10 there were nausea, intense muscular weakness, partial ptosis, diplopia, and great difficulty of speech ; the pulse was 60. Shortly after this the man became unable to speak or to swallow. He made signs for electricity, and, on being asked whether the chemical or the faradic current, indicated the latter, and also the place of application of the electrodes, but was unable to hold one of the latter. Shortly after this, on being raised up, he dropped dead. A fourth case, in which a child five years old died of asphyxia preceded by coma and paralysis as the result of taking a drachm of chloroform-water containing five grains of the extract of conium, is recorded.[4]

In mammals conium produces symptoms parallel with those observed in man, and it probably acts similarly upon all vertebrates.

In frogs convulsions are rarely if ever present ; in birds they are occasionally so ; in mammals they are more frequent,—thus, Ihmsen saw them in twelve out of

* The experiments of Poehlmann (quoted by Husemann[1]) show that very grave symptoms may be induced and yet the pupils remain natural ; but sooner or later they probably always dilate.

twenty-three experiments; they are chiefly clonic, but tonic spasms do occur in the hind legs. As the legs are usually affected before the arms in man, so in quadrupeds the hind extremities are usually paralyzed first. The respiration is generally much affected, and the heart continues to beat after its cessation.

Spinal Cord.—The exact influence of conine upon the *spinal cord* cannot yet be considered absolutely determined, but it is most probable that the poison has a feeble depressant action. Verigo [5] asserts that it is a powerful spinal depressant, and Pelvette and Martin-Damourette [6] say that it acts as an excitant. Lautenbach, in carefully investigating the subject, failed to obtain, under any circumstances, evidences of excitement of the cord; he did succeed in producing loss of reflex activity when the nerve was protected by tying the artery in the limb, but, as in all but two of fifty-two experiments the reflexes in the protected limb were not greatly reduced until just before death, it is plain that any action upon the spinal cord is unimportant and dominated by the more powerful peripheral influences of the poison.*

Nervous System.—Cerebrum.—The retention of consciousness and all the mental faculties almost up to death in conium-poisoning shows that the drug has but little influence upon the general cerebral cortex. According to Lautenbach,[7] the convulsions which occur in the lower animals are, however, of cerebral origin, since after division of the cord they were confined to those portions of the body situated above the section. They are probably asphyxial or of other secondary character.

Nerves.—In 1856 Kölliker [8] announced that the failure of motion in conine-poisoning is caused by a direct action of the alkaloid upon the *efferent* or *motor nerves*. He first experimentally found that in frogs killed by the drug the application of the galvanic current to a nerve fails to induce contractions in the tributary muscles. He then tied the aorta in such a way as to cut off the supply of blood to the hind extremities, and found that after voluntary motion had ceased in the fore legs, and even after galvanic stimulation of the anterior nerves had lost its influence upon the muscles directly supplied by those nerves, irritation of the same anterior nerves produced reflex contractions in the hind legs, showing that the anterior afferent nerves and the spinal cord still retained functional activity after the loss of it in all those efferent nerves reached by the poison. After repeating these experiments a number of times, he drew the conclusion already given.

His experimental results have been confirmed by Funke,[9] by Guttmann,[10] and by Pelvette and Martin-Damourette.† The latter observers extended the series by severing in a frog all the tissues at the upper part

* The experimental results obtained by A. D. Davidson and D. Dyce Brown (*Med. Times and Gazette*, July, 1870), which have been cited as favoring the absurd theory of Harley that the corpora striata are especially affected by the drug, evidently depended upon an arterial anomaly said to be common in the leg of the cat.

† M. Tiryakan (*Compt.-Rend.*, lxxxvi. 1344) has affirmed that absolutely pure conine does not affect the nerves, but M. Prevost (*Arch. Physiol. Norm. et Path.*, 1880, vii.) has shown that chemically *pure* conine bromohydrate has this action.

of the thigh except the nerve, and found that when a batrachian so prepared was poisoned with conine, after the paralysis was complete in all portions of the body to which the poison had access,—after stimulations of the poisoned nerves were powerless to excite contraction in the tributary muscles,—the leg which had been protected from the action of the conine upon it responded not only to irritations applied to its nerve, but also to stimuli placed upon distant portions of the body. These same observers also noted that when conine and strychnine were given simultaneously to a frog from one of whose sciatic nerves the circulation (*i.e.*, direct access of the poison) was cut off in either of the manners spoken of, they produced by their conjoint action a commingling of paralysis in all other parts of the body with violent tetanic spasms in the protected leg,—a commingling explainable only on the supposition that the conine paralyzed all the motor nerves to which it had access through the circulation. Since B. F. Lautenbach,[11] Verigo, A. W. Hofmann, Prevost, H. Schultz,[12] and Fliess[13] have confirmed these experiments, it must be considered as an established fact that the chief physiological action of conine is as a *paralyzer of the motor nerves, and primarily of their peripheral filaments.**

It has generally been believed that conium does not affect the sensory nerves; but in 1875 Gubler[14] called attention to its local influence in benumbing the cutaneous sensibility, and Lautenbach found that when he tied the abdominal aorta and left axillary artery in the frog, and then injected a dose of conine into the abdomen, irritation of the leg whose nerve was not protected from the poison failed to cause reflex movements at a time when irritation of the protected nerves produced reflex actions in distant parts of the body. These experiments seem to show that the alkaloid is a paralyzant to the sensory nerves; but it certainly acts much less powerfully upon them than upon the motor nerves.

Muscles.—All observers agree that in conium-poisoning the muscles themselves are not affected.

Pupil.—The pupil is generally dilated by conine; but both Von Praag[15] and Verigo assert that the phenomenon is not constant, at least in animals. The ptosis of conium-poisoning indicates that the dilatation of the pupil is due to oculo-motor paralysis. The known action of the drug upon nerve-trunks indicates that this paralysis is peripheral,—a conclusion corroborated by the experiments of I. Hoppe[16] and of Lautenbach, each of whom found that when conine is dropped into the eye of an animal it causes at first contraction, apparently due to the intense irritation, and afterwards dilatation, of the pupil.

Temperature.—Verigo, Von Praag, and others affirm that lethal doses of conium cause a decided lowering of temperature; but Lauten-

* H. Tiryakan (*Étude expérim. et chir. sur la Coniine*, Paris Thèse, 1878) endeavors to show that this action of conine is due to an impurity, and not to the alkaloid; but this is *a priori* exceedingly improbable, and Prevost (*Arch. de Physiol.*, Nov. 1880, 40), using the same preparation as did Tiryakan, has found that the motor nerves are affected.

bach asserts that the drug decidedly increases the temperature both when in therapeutic and when in toxic doses.

Circulation.—No sufficient investigation has as yet been made upon the action of conine upon the circulation. Lautenbach states that the arterial pressure falls immediately after the injection of conine, and afterwards rises far above the normal point, and that the pulse is at first accelerated, but afterwards retarded. The secondary rise of pressure is probably due to asphyxia. The primary pulse-acceleration is explained by the observation of Pelénard (confirmed by Prevost) that the pneumogastrics are paralyzed before the motor nerves. Prevost finds that the heart itself is scarcely affected by the poison.

SUMMARY.—The chief symptom of poisoning by conium is a failure of voluntary and involuntary movement, the result of a progressive paralysis of the motor nerves. The cerebrum is not affected, hence consciousness is preserved to the last. The pupil is dilated by a peripheral paralysis of the oculo-motor nerve. The sensory nerves and the spinal cord are probably feebly depressed. It is probable that the alkaloid does not directly act upon the circulatory apparatus except to paralyze the pneumogastrics.

THERAPEUTICS.—The paralytic action of conium naturally suggests its use in spasmodic affections; and accordingly it has been tried in *chorea*, in *paralysis agitans*, in *whooping-cough*, and in other diseases of similar nature. Although it seems not to have met with continued favor, and is but little used, it may be employed when life is threatened by the mere convulsive actions, which it will sometimes temporarily suspend. In *maniacal* and *hysterical excitement*, the drug in full doses is said to produce a highly favorable condition of calm and relaxation; and in the treatment of the insane, conium is much used by some alienists.

Conium was formerly employed to relieve pain or as a deobstruent and alterative in chronic glandular or arthritic diseases, and even in cancer, but for these purposes has passed entirely out of vogue. The belief that it possesses alterative qualities does not seem to be well founded.

ADMINISTRATION.—The preparations of conium are exceedingly uncertain in their action. Conine itself is very prone to undergo spontaneous change, although its hydrobromate is said to be a stable crystalline salt; dose, one-twentieth to one-twelfth of a grain (0.003–0.005 Gm.). The dose of the extract (EXTRACTUM CONII, U. S.) is one grain (0.06 Gm.); of the tincture, one-half to one fluidrachm (2–4 C.c.); of the fluid extract (EXTRACTUM CONII FLUIDUM), one to two minims (0.06–0.12 C.c.): all of which must be administered in increasing doses until some effect is experienced. Of these preparations the last is certainly the best.

TOXICOLOGY.—Sufficient has been said about the symptoms caused by conium. After death from it no distinctive lesions are to be found, only the usual indications of death from asphyxia. The treatment consists in the immediate evacuation of the stomach and the exhibition of

tannic acid,—the tannate formed is, however, probably more or less poisonous,—with the use of external heat and of internal stimulants: artificial respiration should steadily be maintained so long as there is the faintest indication of cardiac action. No physiological antidote is known; but strychnine and other respiratory stimulants should be used.

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FAMILY VII.—RESPIRATORY STIMULANTS AND DEPRESSANTS.

FORMERLY the effect of a drug upon the respiration was universally estimated by its influence upon the rate of the respiratory movement. If this were increased the drug was spoken of as a respiratory stimulant; if it were decreased the drug was a respiratory depressant. It is evident, however, that a drug may increase the rate and yet so diminish the extent of the respiratory movements that the amount of air taken in and out of the lungs would by it be absolutely decreased. Consequently, as was first clearly shown by H. C. Wood, the only proper test as to the effect of a drug upon the respiration is the amount of air moved by the lungs under its influence. (See *Journal of Physiology*, 1892.)

It is worthy of note that the respiratory centre is anatomically a portion of the motor tract of the spinal cord; and this seems to be carried out by its physiological relations with drugs, apparently all substances which are stimulant to the motor side of the spinal cord being centric respiratory stimulants, and those which are depressant to the motor side of the spinal cord being centric respiratory depressants.

The drugs which are practically used as respiratory stimulants are *ammonia*, *caffeine*, *atropine*, *cocaine*, and *strychnine*. For the discussion of these drugs as individual remedies, the reader is referred to the respective articles upon them. Certain comparisons, however, may well be here instituted. H. C. Wood has found that ammonia is too fugitive in its action and too violent in its local influence upon the mucous membranes to be of practical value as a respiratory stimulant. In contrasted experiments atropine appeared to be the most powerful in its influence on the normal animal, but strychnine apparently had more power in asserting its influence against opposition. Thus, although atropine seemed to stimulate respiration more than did strychnine in the normal dog, yet in the chloralized dog the effect of strychnine was distinctly greater than that of atropine. Cocaine was found to be, as a respiratory stimulant, about half-way between atropine and strychnine.

Another result reached was that it was possible to get greater effect by the consentaneous use of two drugs than by one alone. Thus, in the heavily chloralized dog, strychnine given up to the point of incipient tetanus could only raise the respiratory function to a certain height; whereas injections of cocaine, without affecting the tetanoid con-

dition, would increase the air-movements perhaps to the normal or even above it. A practical deduction from this is that in all cases in which respiratory stimulation is urgently needed, at least two alkaloids should be used. In diseases such as *pneumonia* or suffocative *bronchitis* we have found that the alternate use of cocaine and strychnine gives the best results; a dose of each remedy may be given every four hours, the patient receiving one or the other every two hours. In most respiratory diseases the collateral effects of atropine interfere very greatly with its use. On the other hand, in narcosis, especially from opium, the awakening influences of the drug upon the cerebral cortex lend to it especial value; so that usually in narcotic poisons the combination of atropine and strychnine is probably better than that of cocaine and strychnine.

In all cases of severe narcosis the alkaloidal salts should be used hypodermically.

ASPIDOSPERMA. U.S.—QUEBRACHO.

The bark of an evergreen South American tree, Aspidosperma Quebracho-blanco, in which, according to Heine, there are six distinct alkaloids. Of these, probably the most important is *aspidospermine*, discovered by Fraude in 1878.*

Our knowledge of the physiological action of quebracho bark is very imperfect. According to F. Penzoldt,† large doses of the drug cause in

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* The other alkaloids are *aspidospermatine*, *aspidosamine*, *quebrachine*, *hypoquebrachine*, and *quebrachamine*. Their physiological action has been studied to some extent. Harnack and Hoffmann (*Zeit. f. Klin. Med.*, 1884, viii.) find that *aspidospermatine* causes in the frog respiratory paralysis, with palsy of all the striated muscular fibre of the body, including the heart-muscle. Upon mammals it acts very feebly, its most marked influence being upon the respiration. *Quebrachine* acted upon the frog precisely as did aspidospermatine. Its influence upon the mammal was at least twenty times as great as that of aspidospermatine, comparatively small doses producing death by respiratory paralysis. *Quebrachamine* acted very much as did aspidospermatine upon the breathing and upon the muscular fibre. *Aspidosamine* acted upon the breathing and upon the muscular fibre like aspidospermatine, but also paralyzed the motor nerve-endings. Its influence upon mammals was quite feeble. According to this research, the combined alkaloids have especial influence upon the respiration and the respiratory centres, and at the same time affect the muscular fibres directly and the peripheral nerve-endings. Schiffer (*Archiv f. Physiol.*, 1883, 249) has found that the extract of a commercial quebracho-blanco produces in the rabbit general muscular weakness, followed by paralysis with greatly diminished reflexes and an appearance of the deepest narcosis, with increased frequency of breathing, unaltered cardiac activity, and unchanged pupils. After very large doses death occurs in a very short time, preceded by convulsions. The motor nerve-trunks were found even during life almost devoid of functional activity. The exact nature of the bark used for the making of the extract is not stated. Eloy and Huchard (*Archives de Phys. et Path.*, April 1, 1886) found that the extract of quebracho-blanco has some effect on sensibility after the taking out of the quebrachine, hypoquebrachine, aspidospermine, and aspidospermatine, but that these alkaloids themselves have no effect on general sensibility. The four alkaloids named produced paralysis, with, if in excessive doses, tonic convulsions, and all of them had the power of reducing the temperature, quebrachine being in this respect the most active. Aspidospermine increased the amplitude of the respiratory movements to a very marked degree, but in overdose produced irregularity and failure of respiration. The three other alkaloids had much less effect upon respiration.

† *Die Wirkungen Quebrachodrogen*, Erlangen, 1881.

the lower animals motor paralysis, dyspnœa, and finally death from asphyxia. The breathing is said, even in moderate dose, to become slower in rate but deeper, and the blood-pressure not to be affected at all, or after toxic doses only late in the poisoning. It is affirmed that, although death seems to take place from asphyxia, the venous blood always is more or less of the arterial hue; and Penzoldt believes that the relief of dyspnœa obtained clinically by the use of the drug is caused by its increasing the power of the red blood-disks to absorb oxygen, whilst the dyspnœa and fatal asphyxia of quebracho-poisoning are due to its so affecting the red blood-disks that they are unable to give up their oxygen to the tissues. This curious theory does not seem to us proved; the whole subject needs restudy.

There is, however, much clinical assertion that quebracho is a valuable stimulant, not only when the respiration is embarrassed by *emphysema*, *bronchitis*, *chronic pneumonia*, or other complaints mechanically influencing the lung function, but also in *asthmatic*, *uræmic*, and even *cardiac dyspnœa*.

Aspidospermine of commerce is a more or less impure mixture of all alkaloids of the bark, and hence may be considered to represent its activity. Dose of commercial aspidospermine, a quarter to half a grain (0.016–0.03 Gm.); of fluid extract (EXTRACTUM ASPIDOSPERMATIS FLUIDUM, U. S.), a quarter to one fluidrachm (1–4 C.c.); of solid extract, one to three grains (0.065–0.194 Gm.).

ORDER II.—CARDIANTS.

FAMILY I.—CARDIAC STIMULANTS.

THE term cardiac stimulants is here used to designate a number of medicines which, when given internally, increase the power and force of the circulation, and are used by the physician for such purposes. There are some substances which are heart-stimulants in reality, but which possess other properties in so great a degree as to overshadow their cardiac relations, and are not used by the physician to affect the circulation. Such medicines are considered in connection with those powers which give them their clinical value, and are consequently not included in the present class. Some of the members of this class are slow in their operation, some more rapid. Some produce increase in the pulse-rate, some lower it. It is evident, then, that no general indications can be laid down for their use, but that medicines so diverse must be studied individually.

AMMONIA.

Ammonia is a colorless, irrespirable, highly irritant gas, of a strong alkaline reaction, extremely soluble in water. It is obtained upon a large scale as a waste product in the manufacture of coal-gas, and is official in watery and alcoholic solutions and in various salts.

PHYSIOLOGICAL ACTION.—*Local Action and Elimination.*—In solution, ammonia is a very powerful irritant and even escharotic, producing, if kept in contact with the skin, blistering, and finally sloughing, and causing the most serious disturbances of mucous membranes which it reaches. This local action is sufficient to interfere with its absorption, and it is difficult to produce distinct constitutional symptoms with it in man. Its volatility and the extreme fugaciousness of its action would seem to indicate its elimination by the lungs ; but Feltz and Ritter[1] fail to find it in the breath of poisoned animals, and Bence Jones[2] believed that at least a portion of it is oxidized in the system, basing this belief on the facts that it seems to heighten the acidity of the urine and that he has found an excess of nitric acid in the urine after an exhibition of the ammonia itself, its tartrate, carbonate, or muriate. The theory that some portion of the ammonia is, in conjunction with carbonic acid, converted into urea is held by many physiologists.*

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* This theory is of such purely physiological interest that it is dismissed with the following key to the literature: *Arch. f. Exper. Path. u. Pharm.*, ii., viii., x. 125, xii. 77; *Zeitschr. f. Physiolog. Chem.*, ii. 29, iv. 36; *Zeitschr. f. Biol.*, xiv.

General Action.—When ammonia is injected into the veins of animals in considerable quantities, it causes violent convulsions, with remarkable disturbance of the respiration, followed, if the dose has been large enough, by death in a very short time.* Billroth[3] states that the temperature falls enormously in animals poisoned with ammonia.

Cerebrum and Spinal Cord.—Ammonia has no effect upon the cerebrum. The tetanus produced by it in the lower animals is accompanied by great increase of the reflex activity (Funke[4]), and is certainly of spinal origin, since it occurs below a section of the spinal cord (Lange) and is not prevented by tying the artery of a limb (Funke). It would therefore appear that the toxic dose of ammonia is a powerful stimulant to the motor spinal cord. Upon the sensory cord it seems to have little or no action.

Respiration.—The intravenous injection of ammonia causes in the animal a great acceleration of the breathing, which after large doses may be preceded by temporary arrest of respiration in expiration. The cause of this arrest is uncertain, Funke observing it after section of the vagi, while in the experiments of Lange it was always absent. Section of the vagi, however, does not interfere with the increased rapidity of the breathing, the change from the deep breathing of divided vagi to the extremely rapid respiration of ammonia-poisoning being colossal (Funke). Further, Binz[5] has found that the increase of the respiratory rate in chloralized rabbits is accompanied by a great increase in the amount of air breathed. Ammonia is, therefore, a powerful direct stimulant to the respiratory centres.

Circulation.—Both in normal and curarized animals intravenous injections of ammonia produce a very decided rise of the arterial pressure, which, according to Lange, takes place after division of the cord and consequent separation of the arterioles from their vaso-motor centres. The rise of pressure must, therefore, be due to an action either upon the heart itself or the peripheral vessels. The probabilities are that the drug acts both upon the heart and the muscular fibres in the coats of the arteries. The rise in the arterial pressure is followed, if the dose has been large enough, by a decided fall, ending in permanent diastolic arrest of the heart. Probably upon both heart and muscular fibres in the walls of the arterioles ammonia acts, first as a stimulant and then as a depressant or paralyzant. The pulse-rate is very much increased by ammonia; this increase, according to Lange, not occurring after section of the spinal cord. If this be correct, the increased pulse-rate would seem to be due to an action upon the cardiac accelerators. In both man and animals intravenous injections of ammonia are liable to be followed by a sudden temporary fall of pressure, due to the action of the concentrated drug upon the heart.

* F. Lange (*Archiv f. Experiment. Path. u. Pharm.*, ii. 368), V. Feltz et E. Ritter (*Journal de l'Anatomie et de la Physiol.*, 1874, 326), and Funke (*Pflüger's Archiv*, ix. 426).

According to Feltz and Ritter, the blood of a dog killed by ammonia is incapable of absorbing oxygen, and contains much less than the normal amount of gas, whilst the red disks resist the action of acetic acid to a markedly abnormal degree.

THERAPEUTICS.—Externally, ammonia is much used as a constituent of irritating liniments, and, on account of its efficiency and cheapness, is very valuable. By inverting a watch-glass full of the stronger water of ammonia upon the skin, a blister may be raised in a very few minutes; but, as the effects of the application are apt to be severe, the use of it is justifiable only under rare circumstances.

Internally, the chief indication for the use of ammonia is *failure of the heart's action*. The more sudden and purely functional this is the more efficacious is the remedy, which should in such cases be not only administered by the stomach, but also inhaled through the nostrils, as the local action of the irritant vapor upon the mucous membrane has a very arousing influence. When the failure of the circulation depends upon a slow and persistent cause, as in *adynamic fevers*, ammonia is not generally useful, but may be employed as an adjuvant to alcohol in the crisis of the disorder. As a stimulant, ammonia may be useful in poisoning by venomous serpents, but the statements that have been made that it is antidotal to venom have no foundation. (For detailed discussion, see the tenth edition of this treatise.)

In failure of the heart from anæsthetics* or other poisons, animal or vegetable, in *sudden collapse* in disease, as is sometimes seen in the *exanthemata*, in *cholera*, and not rarely in *pernicious malarial fever*,† or after *surgical operations* or *injuries*, hypodermic injections of ammonia‡ have seemed to be in a number of reported cases of very great service. It is probable that in many of these instances they have largely acted as local irritants, reflexly exciting the heart. From fifteen to twenty-five minims of the aqua ammoniæ fortior, diluted with four times its bulk of water, should be thrown directly into a vein of the arm, and repeated in fifteen minutes if necessary.

Ammonia appears to have a tendency to act upon the mucous membrane of the lungs, and its salts are used as stimulant expectorants in adynamic pectoral inflammations, as in typhoid *pneumonia*. As a stimulant antacid, it is frequently of service in cases of *headache* from *gastric acidity*.

TOXICOLOGY.—Ingested in large amount, ammonia acts as a violent corrosive poison, the symptoms of its constitutional action being entirely lost in those caused by its local influence. Violent pain in the

* Ringer (*Practitioner*, xxvii.) finds that ammonia added to the frog's heart depressed with chloroform, iodoform, etc., has a pronounced effect in re-establishing its action.

† See Zuelzer (*Revue de Thérap. Méd.-Chir.*, July 1, 1872).

‡ See *Indian Med. Gaz.*, June 1, 1872; *Med. Times and Gaz.*, Nov. 1872; *Chicago Med. Journ.*, 1872; *London Med. Record*, 1873, i.; *L'Abeille Méd.*, Aug. 1874; *Berlin. Klin. Wochenschrift*, No. 24, 1874; *Archives Gén.*, 1874, ii.; *Lancet*, 1879, ii. 158; *New York Med. Rec.*, xv. 532.

mouth and fauces, in some cases intense burning in the larynx with sense of choking, with great difficulty of breathing and rapid asphyxia; more commonly violent abdominal pain, vomiting, bloody purging, and other symptoms of gastro-enteritis, mark its escharotic effects. Death from œdema of the larynx may occur within five minutes. More commonly the fatal result is wrought out more slowly, with collapse and sometimes convulsions secondary upon the local effects. In some cases symptoms of impending suffocation, resulting in death from asphyxia, have occurred, and at the autopsy intense redness and congestion of the bronchial mucous membrane have been present, due no doubt to the irritant's having found its way into the bronchi. The intellect may be clear to the very moment of death, or stupor, and finally coma, may be developed. If the victim survive for a few hours recovery usually occurs, but the convalescence is commonly protracted, and permanent ill-health may result from the destructive lesions produced by the poison. These lesions are to be found not only in the respiratory and gastro-intestinal tracts, but also in the kidneys.[6] The treatment of poisoning by ammonia consists in the neutralization of the ammonia as soon as possible by vinegar or other dilute acid, and the meeting of indications as they arise. If the œdema of the glottis be threatening, tracheotomy should at once be performed.

ADMINISTRATION.—There are four official preparations of uncombined ammonia,—namely, AQUA AMMONIÆ FORTIOR (Stronger Water of Ammonia), sp. gr. 0.901; AQUA AMMONIÆ (Water of Ammonia), sp. gr. 0.960; SPIRITUS AMMONIÆ (Spirit of Ammonia); and SPIRITUS AMMONIÆ AROMATICUS, or Aromatic Spirit of Hartshorn. To reduce the strength of the first of these preparations to that of the second or third requires the addition of one and eight-tenths measures of water. The aromatic spirit contains both ammonia and its carbonate. For hypodermic use a water of ammonia or a solution of the ammonium carbonate is to be preferred. Dose of the water or either spirit, twenty-five drops to a teaspoonful (1.5–3 C.c.), properly diluted.

Ammonium Carbonate, U. S. (AMMONII CARBONAS), is the best preparation for continuous use. It occurs in white, translucent, fibrous masses, which on exposure become opaque and efflorescent, parting with ammonia and passing into a bicarbonate. It is soluble in four and a half times its weight of water, and may be given in solution in doses of from five to ten grains (0.3–0.6 Gm.), repeated *pro re nata*. The effects of a single dose upon the system probably do not last over one hour.

Ammonium Nitrate (AMMONII NITRAS, U. S.) is official for the preparation of nitrous oxide; Ammonium Chloride (AMMONII CHLORIDUM, U. S.) will be considered under Expectorants; Ammonium Iodide (AMMONII IODIDUM, U. S.) under Alteratives.

ALCOHOL. U. S.

ALCOHOL ABSOLUTUM, U. S. (Absolute Alcohol),—*i.e.*, ethyl alcohol containing not more than one per cent. by weight of water,—is a colorless,

volatile liquid, boiling at 172° F., not congealed by a cold of —166° F., and having the specific gravity of 0.797. It is used only for chemical purposes. ALCOHOL, U. S., contains 94 per cent. by volume of absolute alcohol, and has the specific gravity of 0.820; ALCOHOL DEODORATUM, U. S. (Deodorized Alcohol), contains 95.1 per cent. by volume of alcohol, and has the specific gravity of 0.816; and ALCOHOL DILUTUM, U. S. (Diluted Alcohol), contains 48.6 per cent. by volume of absolute alcohol, and has the specific gravity of 0.936.

Alcohol also exists in the official SPIRITUS FRUMENTI, or WHISKEY, and SPIRITUS VINI GALLICI, or BRANDY, which are obtained respectively by the distillation of fermented grain and of fermented grapes, and should contain from forty-eight to fifty-six per cent. of absolute alcohol, and in the official VINUM RUBRUM, or *Red Wine*, and VINUM ALBUM, or *White Wine*. For medicinal use, brandy should be at least four and whiskey at least two years old.

Local Action.—Alcohol is actively irritant to mucous membranes or other interior tissues with which it may come in contact. It is also very distinctly antiseptic, and has when in concentrated form the power of killing all protoplasms.

Alcohol is formed out of sugar by fermentation; but, as a discussion of the natural history and chemistry of this process, to be of value, would occupy much space, the reader is referred for it to works especially devoted to chemistry and to materia medica.

Absorption and Elimination.—Alcohol is absorbed with great rapidity by the stomach, but, as has been shown by Von Mering,[1] is also hurried on into the intestines. It is without doubt taken up freely into the whole length of the alimentary tract. In Baum's[2] experiments symptoms of intoxication appeared in a horse fifteen minutes after its injection into the rectum. (For a study of the point of elimination in the system, see page 282.*)

General Action.—The phenomena which follow the ingestion of alcohol are, unfortunately, so well known as to make any description of them here unnecessary, and we shall at once proceed to the discussion of the action of the drug upon different portions of the organism.

Nervous System.—We have not met with a close experimental study of the order in which the nervous centres are affected, but it is scarcely doubtful that alcohol acts upon them as does ether, except that the latter substance, being much more volatile than alcohol, is consequently absorbed and eliminated much more rapidly, so that its influence is more evanescent. We know by experiment that the vapor of alcohol is capable of producing the stupor known as anæsthesia, and, further, that this anæsthesia may be deepened into death, accompanied by all the phenomena of fatal ether-narcosis. It is probable that there is an early stage in the action of alcohol in which not only the cerebral but

* See Chittenden, Mendel, and Jackson (*Amer. Journ. Physiol.*, 1898, i.).

it may be even the spinal centres are stimulated, but certainly in the advanced stages of alcohol-poisoning muscular relaxation and the loss of reflex activity are altogether or in part due to the sedative influence upon the motor cord. The theory of a primary stimulation gains plausibility from the experiments of Mommsen,[3] in which it was found that the excitability of the peripheral motor nerve is primarily increased by the local action of alcohol. The observation of Dogiel, that in the alcoholized dog both sensory and motor nerves are markedly depressed, without doubt holds good for acute alcoholism in man. Whether this depression is due directly to the alcohol or to the changes produced by it is uncertain. It cannot be denied that the continuous effect of large doses of alcohol upon the nervous tissue is depressant.

The original experiments of Heinrich Dehio,[4] showing that changes can be demonstrated in the ganglionic cells of the brain in animals killed by the large dose of alcohol, have been repeated and extended by Colin C. Stewart[5] with corroborative results.

Circulation.—When alcohol is given to healthy men, it increases the frequency, and we believe also the force, of the pulse.

Experiments made upon the lower animals have yielded results which at first sight appear somewhat contradictory. When, however, the different effects of different doses of alcohol are clearly distinguished, most of the apparent contradictions disappear. Thus, the results obtained by H. Zimmerberg, who found that alcohol reduces both the rate and force of the pulse, evidently depended upon his employing toxic doses of alcohol. The same objection holds with the experiments of Z. Gutnikow,[6] in which were given to dogs doses of two hundred and fifty grammes * of from fifty to seventy per cent. alcohol, with a marked fall both in the arterial and in the venous pressure. There was also in Gutnikow's observations a fall in the intra-cardiac pressure, both auricular and ventricular. In some cases the intra-cardiac fall preceded the fall of the arterial pressure. In the experiments of J. Dogiel, and similarly in those of J. D. Castillo,[7] small doses of alcohol produced marked increase of the arterial pressure, an increase which was followed, when the dose was large enough, by a fall of the arterial pressure. This result is in general accord with that obtained by S. Potts Eagleton.[8] †

It would appear, for reasons just given, that alcohol in small dose increases arterial pressure, and in the experiments of Castillo and of Eagleton this rise was not prevented by previous division of the pneumogastric, accelerators, and spinal cord ; it would seem, therefore, to be due either to a direct action upon the heart itself or upon the walls of the arterioles. According to the experiments of Castillo, the work of the isolated heart of the frog is increased by the small dose of alcohol : so that

* The weight of the dogs is not given, and the amount per kilo, therefore, cannot be estimated.

† Eagleton's experiments were made with a continuous injection of alcohol, and in two of them the results were somewhat different from those ordinarily obtained. The reason of this is not obvious. None of his dogs appear to have been curarized, and the peculiar method of experimentation requires the results to be interpreted with great care.

it would appear that alcohol is a *direct stimulant to the heart.** The fall of the arterial pressure caused by the large dose of alcohol occurs after section of the cord, and must, therefore, at least in part, be due to direct action upon the heart itself or muscle-fibres in the vessel-walls, a conclusion which is in conformity with the experiments of Castillo, in which stimulation of a sensitive nerve caused rise of pressure, proving that the vaso-motor system was still capable of responding to stimuli. Certainly the known action of alcohol upon the excised frog's heart, and the diastolic arrest produced by it in the mammal, prove that *in overdose alcohol is a direct depressant to the heart;* nevertheless, there can be little doubt that it exerts a similar *depressing influence upon the muscle-fibres in the walls of the vessels;* indeed, there is much reason for believing that at a time at which the heart is still under alcoholic stimulation the blood-paths are widened out, for John C. Hemmeter[9] has found in experiments made with Ludwig's stromuhr that alcohol may increase the velocity of the blood-current. Unfortunately, Hemmeter does not give the amount per kilo of alcohol used in his experiments, and does not seem to have experimented with varying doses.†

* In apparent opposition to this conclusion and the experimental and clinical evidence upon which it is based are the results obtained by Martin (*Maryland Med. Journ.*, x. 292) in experiments made upon the dog's heart, isolated by a long and complicated procedure invented by himself,—experiments which have been repeated with similar results by J. C. Hemmeter (*Johns Hopkins Univ. Stud. Biolog. Labor.*, iv.). Martin found that blood containing one-eighth per cent. by volume of absolute alcohol has no immediate action upon the isolated heart; that blood containing one-fourth per cent. diminishes within a minute the work done by the heart; and that blood containing one-half per cent. always diminishes remarkably the heart-work, and sometimes nearly destroys it, so that not enough blood is pumped out of the left ventricle to supply the coronary artery. The curious observation was made that cutting away the pericardium stopped the action of even one-half per cent. of alcohol. The explanation of this, offered by Martin, is that alcohol so relaxes the cardiac muscle that there is not room in the pericardium for a full diastole, the relaxed heart being, even in its systole, about sufficiently large to fill the pericardium. This explanation is hardly satisfactory. Can there be a local inhibitory cardiac apparatus, with peripheral filaments in the pericardium which are irritated by alcohol, and whose removal prevents the action of the alcohol?

It seems to us at present not possible satisfactorily to examine the results obtained by Martin. Hemmeter suggests that they may be due to alteration produced by the alcohol in the defibrinated blood, but this hardly suffices. The subject is made more difficult by the observation of Hemmeter, that under the influence of alcohol intra-cardiac regurgitant murmurs are developed in the isolated heart, which further suffers from hemorrhages into its tissue,—results, we believe, never seen in alcoholic intoxication.

† The velocity of the blood-current in the arterial system depends upon the relations between the propulsive force and the resistance: the greater the propulsive force the greater the velocity, the greater the resistance the less the velocity. (The term velocity is here used to express the amount of blood passing a given point in a given length of time.) It will be seen at once that the arterial pressure and velocity are not synonymous or necessarily accordant. If, for instance, a drug increases the resistance without affecting the propulsive force, the blood-pressure may be raised or remain almost unchanged while the velocity will decrease. Hemmeter gives the following as possible variations to which the main factors in the making of velocity and arterial pressure are subject:

1. The energy of the heart contractions remains the same and the resistance (*a*) increases, then blood-pressure increases and velocity decreases. (*b*) Resistance decreases, then blood-pressure decreases and velocity increases.

2. The energy of the heart activity increases and the (*a*) resistances are the same, then blood-pressure and velocity increase. (*b*) The resistances increase, then blood-

Dogiel, in his experiments, found that under the action of alcohol the pulse-rate is first increased, then diminished, and then increased. Both Castillo and Eagleton have noticed also primary increase in the rate of the cardiac pulsations,—an increase which Dogiel attributes to stimulation of the accelerator nerve, but which Castillo has found occurs in the mammal when the heart has been isolated after section of the cord, and which Eagleton has noted in the excised frog's heart. Present evidence indicates that alcohol in moderate dose acts as a *direct stimulant to the rate* as well as to the force of the heart's beat. Large doses have been noted by various observers to lessen pulse-rate in the animal, but certainly, in the human system, slowing of the pulse is not a distinct phenomenon of alcoholic poisoning.

Blood.—There seems to be little reason for supposing that alcohol in therapeutic dose has an appreciable effect upon the blood, but as long ago as 1841 C. H. Schulz [10] observed that mixed with the blood outside of the body it not only causes coagulation, but also separation of the hæmoglobin from the corpuscles. It is probable that to the action of the alcohol upon the hæmoglobin is due the fact noted by Schmiedeberg [11] that alcohol mixed with blood lessens its ability to yield oxygen in the presence of a reducing agent. Jaillet and Hayem state that in rapid alcoholic poisoning in animals extensive alteration in the blood-corpuscles can be discovered, many of these bodies being shrivelled and altered in form, with yellow precipitates of hæmoglobin in their interior.

Temperature.—Owing no doubt to the sensations of warmth induced by its local action on the stomach and by the increased activity of the circulation in the extremities, alcohol was formerly looked upon as a promoter of animal heat. This view was questioned as early as 1848 by Duméril and Demarquay, and has been studied and written about to an enormous extent. The matter has been so thoroughly worked out that it does not seem wise to do more here than give results, and to refer the reader who is desirous of following up the literature of this subject to the tenth edition of this treatise.

In the lower animals small doses of alcohol produce an increase of the bodily temperature, which rarely in mammals reaches more than 1° F. and in birds 1° F. Larger doses of alcohol produce a fall of temperature in the animal proportionate to the size of the dose. According to Ruge,[12] when the dose has not been sufficient to cause distinct intoxication, the fall usually amounts to from $\frac{1}{5}$° C. to $\frac{3}{5}$° C., rarely reaching one degree. When there is distinct narcosis the fall may amount to 3° C., or with a lethal dose to 5° C. Bouvier and other observers have found that the effects

pressure increases and velocity remains the same. (*c*) The resistances diminish, then blood-pressure remains the same and velocity increases.

3. The energy of the heart activity decreases and at the same time (*a*) the resistances are the same, then blood-pressure and velocity are reduced. (*b*) The resistances are correspondingly greater, then blood-pressure remains the same and velocity decreases. (*c*) The resistances are correspondingly smaller, then blood-pressure sinks and velocity is the same.

of large doses of alcohol are even more marked in animals suffering from pyæmic fever ; the reduction of temperature may amount to 8.5° C., and the fever be altogether put aside by the narcotic dose. The effect of alcohol upon the temperature in man is parallel to that which is produced in the lower animals ; the fall from large doses is, however, less pronounced, probably because the cerebrum of man is proportionately much more sensitive to alcohol than is that of the animal, and narcosis results from smaller doses of the poison. Again, in persons accustomed to the use of alcohol the elevation of the temperature does not appear ; and, indeed, it cannot always be produced in a normal subject. Further, the habitual use of alcoholic stimulants greatly lessens the depressing influence of alcohol upon the bodily temperature, so that the temperature of the drunken man is not always below the normal. As, however, intoxication becomes more profound the tendency to a fall of temperature is more and more marked.

The fall of temperature produced by alcohol is largely due to an excessive loss of heat, but the relations of alcohol to thermogenesis form such an integrant portion of its action on nutrition that its discussion will be postponed to that heading.

Respiration.—According to the experiments of Binz[13] and of A. Jaquet,[14] small doses of alcohol increase the number and amplitude of the respiratory movements. The contention of Jaquet, that this increase is due to the local irritation caused by the alcohol, is certainly not proved by him, and does not seem probable, since it has followed the intravenous use of the drug. The toxic dose of alcohol produces centric respiratory paralysis, and it would appear, therefore, that the poison stimulates or paralyzes the respiratory centres, according as it is in small or large amount.

Relations of Alcohol to Nutrition.—In studying the relations of alcohol or other drugs to the general bodily nutrition, the subject naturally divides itself into two parts, the first relating to the nutrition which has to do with the production of animal heat and of affording force for the needs of the system ; the second, that which has to do with the building up of tissue and the chemical movements of protoplasm. The action of a drug upon heat-production in the body can be directly studied by means of proper calorimeters, or it can be studied indirectly by chemical examination of the amount of oxygen consumed and of carbonic acid produced in the organism.

The first calorimetrical studies upon alcohol were those by Bevan Lewis.[15] He found that in the rabbit alcohol sometimes produces a primary lessening of heat-production, most marked and pronounced after small doses, followed by a marked increase in heat-production, most pronounced after large doses of alcohol. In five observations by E. T. Reichert and H. C. Wood upon dogs, the average results were in accord with those by Bevan Lewis, although their individual experiments yielded somewhat varying results. In some of these experiments heat-dissipation more than kept pace with the increase of heat-production, and the bodily temperature fell. In other instances the bodily temperature rose, showing that heat-production was

increased more than heat-dissipation. In a further series of experiments E. T. Reichert[16] obtained, in five experiments, increased heat-production, and in thirteen decreased heat-production, the difference not depending upon dose, and the range of variation of result being as much as sixty-five per cent. For a complete discussion of the matter, the reader is referred to the paper of Reichert.

The discordant results obtained by calorimetrical studies appear to prove that the action of alcohol upon thermogenesis is complex and varying, and that, therefore, it is probably in great part indirect. The alterations of heat-production are probably in large part secondary upon disturbances of heat-dissipation, the more recent researches confirming the conclusion which we had previously reached, "that the great fall of bodily temperature which occurs after toxic doses of the drug is due to excessive heat-dissipation, which in turn is the result of vaso-motor paralysis." A further corollary is that our present evidence, derived from calorimetrical studies, indicates that alcohol does not pronouncedly and directly affect those nutritive processes through which the animal heat is maintained.

The effect of alcohol upon the elimination of carbonic acid by the lungs has been investigated by several observers, with different results.

According to the researches of Böcker,[17] of N. S. Davis,[18] of Hammond,[19] of Perrin,[20] of Boeck and Bauer,[21] and of Rumpf,[22] there is a lessening in the amount of carbonic acid gas exhaled; on the other hand, E. Smith[23] found that small doses of alcohol increased the elimination of the gas, although brandy, whiskey, and gin always lessened the production. Henrique[24] found in himself that the consumption of oxygen was increased by alcohol. Wolfers[25] noted in the rabbit an increase both of the oxygen ingestion and of the carbonic acid elimination. Bodländer[26] found that in rabbits and dogs alcohol produced a decrease of the oxygen consumption and carbonic acid production, whilst in man Zuntz[27] obtained an increase in carbonic acid production, and Geppert[28] no important effect. The oxidation of the alcohol itself must, of course, yield carbon dioxide, but in amount too small to be appreciable.

In the older researches of Boeck and Bauer the result was arrived at that whilst small doses of alcohol diminish oxygen consumption, large doses increase it, and it is possible that the different results which have been obtained by investigators, as just quoted, may depend somewhat on the doses used by them. Nevertheless, the divergency seems at present not capable of being cleared up by such a supposition. If alcohol really did have a direct powerful influence upon oxidation in the general system the conclusions of investigators should be more in accord, and it would seem, therefore, probable that any influence which the drug may have is indirect, or is so feeble as to be set aside by various accidents, circumstances, or happenings; possibly even by other actions of the alcohol itself. This conclusion is in accord with that which has been reached calorimetrically, and the best expression of the present state of our knowledge is *that it is not probable that alcohol has any pronounced positive influence upon the processes of oxidation or of heat-production in the system.*

The determination of the action of the drug upon the chemical movements of protoplasm, and the destruction of albuminous materials in the body, is of course to be made by a study of its effect on the nitrogenous elimination.

Among the earliest students, Böcker is commonly believed to have experimentally determined that it lessens the excretion of urea. We have seen only an abstract of the original paper; in it this is not positively asserted, but seems to be inferred. Hammond has performed a very elaborate series of experiments upon himself: first, when just sufficient food was taken to maintain the weight of the body; secondly, when more than enough for that purpose was ingested; thirdly, when not enough was taken. Under all these circumstances, urea, chlorine, and phosphoric acid were lessened in amount by the ingestion of alcohol. Parkes and Wollowicz[29] affirm that their experiments gave a contrary result. In examining the reports of their experiments we find, however, that on one of the days the man taking the alcohol had a chill followed by fever. If this day be omitted, the average daily excretion of urea during the alcoholic period was 34.35 grammes; during the time when brandy was taken, 34.8 grammes; and during the water period, 35.02 grammes. The ingestion of alcohol seems, therefore, to have reduced the elimination of urea by about ten grains a day. In the experiments of L. L. Riess[30] upon two persons without analysis of food or fæces, the exhibition of alcohol was followed by great lessening of the excretion of urea, and, to a less pronounced degree, of uric acid, chlorides, phosphates, and sulphates, and at the same time an increase of the bodily weight. H. Keller[31] made experiments upon himself. The prodromic period was three days; alcohol, one day; after-period, three days. The result was a fall of 1.4 grammes in nitrogen elimination during the alcohol day, with an increase in the after-period of one gramme above the normal. No examination of the fæces was made.

It is very properly objected to all the experiments thus far quoted, that no note was taken of other nitrogenous elimination than that through the kidneys. In 1878 Munk[32] experimented upon dogs with great care to obtain nitrogenous equilibrium, using alcohol in both small and large doses and analyzing both urine and fæces. The result arrived at was that small doses of alcohol (less than 1.5 C.c. absolute alcohol per kilo) diminished slightly the nitrogenous output, whilst larger doses (over 2 C.c.) increased the elimination. The chief objection to Munk's experiments seems to be the short time in which alcohol was used,—three to five days.

In experiments made upon dogs by Charles Norris, Jr., and E. E. Smith, in Chittenden's laboratory in Yale University,[33] the alcohol period was from eight to ten days. The results were: in Experiment No. 1, 1.9 C.c. alcohol per kilo being given, the nitrogenous output was increased two per cent.; Experiment No. 2, 2.3 C.c. per kilo being given, decrease in nitrogenous elimination somewhat less than two per cent.; Experiment No. 3, 2.7 C.c. per kilo being given, decrease about nine per cent. Weiske and Flechsig are stated, in the memoir just spoken of, to have found in an experiment lasting thirty-two days that in a sheep sixty grammes daily of alcohol produced no distinct effect on the daily output of nitrogenous material, there being, in fact, an increase under the influence of alcohol of 0.5 gramme. Z. Donogány and N. Tibald[34] find that moderate doses of alcohol increase nitrogenous elimination.

The results just epitomized are so varying and the changes in the nitrogenous elimination noted so slow and inconsistent, that the accounting for differences by the theory of difference of dose is not plausible; and it seems to us that the conclusion of Chittenden is correct, that so far as our present knowledge goes it does *not seem probable that alcohol has a*

direct specific influence upon nitrogenous elimination,—that is, upon the chemical movements of protoplasm,—a conclusion which, it should be remembered, is corroborated by the experiments of Stammreich and Miura.

A substance may very well have no specific relation with tissue changes and yet be capable of acting as a food which will supply force to the animal organism. From the time of Liebig's celebrated classification of food until the appearance of the memoir of Lallemand, Duroy, and Perrin, ingested alcohol was almost universally believed to be burnt up in the body. These latter observers asserted, however, that alcohol escapes unchanged from the body, not only because they were unable to detect in the blood or tissues any of the results of its oxidation, such as aldehyde or acetic acid, but also because they found alcohol unchanged in the expired air, in the sweat, and especially in the urine. The results obtained by the French investigators were, however, seriously questioned by E. Baudot,[35] who demonstrated that the chromic acid test which Duroy and Perrin had relied on for detecting alcohol in the excretions is so delicate as to reveal .165 grain of alcohol in a quart of water ; and Baudot further affirmed as the result of twenty experiments that, except after immense doses, the amount of alcohol eliminated by the kidneys is so small as practically to amount to nothing.

In 1866 Schulinus,[36] by a very elaborate and laborious investigation, confirmed the results of Baudot, showing that alcohol taken into the blood finds its way by exosmosis into all organs in similar proportion, and does not escape through the kidneys unless in very trifling amounts. In several experiments he found that one-fourth of the ingested alcohol had disappeared from the body after from two to three and one-fourth hours, and, as but a fractional portion of the lost amount was eliminated, he concluded that it must have been burnt up. Adolph Lieben[37] has in a number of experiments arrived at results similar to those of Schulinus.

In 1865 a number of experiments yielded to Anstie,[38] of London, similar results, and also demonstrated that the elimination from the lungs is exceedingly trifling. Thudichum[39] investigated the matter on a large scale in 1864, and again with the assistance of Dupré in 1866. In order to avoid the fallacies of the chromic acid test, the alcohol was obtained from the urine by repeated distillations. In the first instance forty-four bottles of wine, containing four thousand grammes of alcohol, were drunk by thirty-three men, out of whose urine, collected during the next six hours, ten grammes, or only 0.25 per cent., of the ingested alcohol were recovered. In the experiments of 1866 the process was substantially the same, but, greater care being taken to get absolute accuracy and to avoid loss during distillation, 0.82 per cent. of the amount administered was found in the urine. Subbotin[40] has made an apparently close experimental study of the subject upon six rabbits, and has shown that elimination continues for a longer time than had been generally believed, and that twice as much of the alcohol escapes by the skin and lungs as by the kidneys. In one experiment he found that sixteen per cent. of the alcohol escaped unchanged in the first twenty-four hours ; elimination after this time, although perceptible, amounted to very little. As he, like Lallemand and his colleagues, experimented with poisonous doses, his results confirm rather than contradict those of Baudot, Schulinus, Anstie, Thudichum, and Dupré ; for it is manifestly evident that after such doses elimination would be proportionately greater than after smaller quantities, as there naturally must be a limit to the powers of the system to oxidize alcohol. R. D. Edes,[41] in his experiments, found that after small doses the amount of elimina-

tion by the breath is greater than that by the kidneys, although the contrary holds where large amounts have been administered; in either case the total amount eliminated was but a small percentage of the amount ingested.* Finally, Anstie[42] has repeated his experiments, using the method of Subbotin, and even subjecting a dog, which had been taking for some days very much larger amounts of alcohol than he had eliminated by skin, kidneys, rectum, and lungs, to distillation, with the results of confirming his first experiments and of finding no "residual alcohol" —*i.e.*, alcohol left in the body—worthy of mention. In an elaborate research, Guido Bodländer[43] found that he himself, after the use of alcohol in various quantities, eliminated by the kidneys about 1.2 per cent. and by the lungs about 1.6 per cent.; while in dogs he recovered from the breath about 2 per cent., from the urine 1.6 per cent., and from the skin 0.14 per cent. of the ingested alcohol. He failed entirely to find alcohol in the intestinal excretions, and also, contrary to Lewald's observation in 1857, in the milk of a goat to which nearly a quart of brandy had been given. F. Strassman[44] found 5.21 per cent. eliminated by the breath and 7.89 per cent. by the kidneys, leaving 87 per cent. as the amount destroyed in the organism. A. Benedicenti[45] finds that an increase in the amount of ingested alcohol does not greatly influence the elimination through the lungs, but that lowered temperature markedly lessens such elimination.

These concurrent investigations† certainly demonstrate that but a small proportion of ingested alcohol is either eliminated from or accumulated in the body, and consequently that it must be oxidized in the body. It has been objected to this that no one has as yet been able to detect‡ in the blood any of the ordinary products of its oxidation; the probable reason of this is, however, that the oxidation is carried, as it were, at one bound to its ultimate end, the production of water and of carbonic acid. A strong corroborative proof that alcohol is largely consumed in the body is furnished even by the experiments of Lallemand, Duroy, and Perrin, for they proved that elimination ceased, or at least could not be detected by the most delicate tests, *before* the alcohol had all escaped from the body.

A further confirmation of the theory that asserts the oxidation of alcohol in the body is found in the researches of H. Ford,[46] whose experiments, if accurate, demonstrate that alcohol is formed in the body out of hepatic sugar. Unfortunately, these experiments have as yet not been repeated.

Working on a very large scale, by the distillation of the blood of animals, Ford obtained in weighable quantities a substance which he believed to be alcohol.§

* Edes relied upon the chromic acid test, which Binz asserts to be fallacious. In the experiments made by Stenbach and Schmidt, under Binz's direction, alcohol could not be detected in the breath, and Binz believes that no elimination of it occurs from the lungs. He declares that the odor of the breath after drinking is not that of alcohol, but of the ethers and other volatile principles of the various liquids imbibed.

† We believe that these results have also been confirmed by Wöhler (*Journal des Progrès*, xi.), but we have not seen the original paper or any abstract of it.

‡ Duchek (*Vierteljahr. f. Prakt. Heilk.*, 1853, iii.) did not, as he thought, demonstrate the presence of aldehyde in the blood of animals poisoned with alcohol.

§ Space is wanting to describe in detail the very elaborate methods employed by Ford. The tests which he relied on, to prove that the liquid obtained was alcohol, were the chromic acid test, the peculiar inflammability, and the optical appearance of the alcohol in the conducting-tubes at the time the distillate commenced to boil.

Further, Ford distilled various tissues, also blood from the lungs and liver. He also made elaborate calculations, based on the carbon ingested and on the carbon exhaled, as to the amount of alcohol which ought to be found in the capillary blood of the lungs. The results are expressed in the following table:

Alcohol in the capillary blood of the lungs:

	calculation based on *carbon ingested*	0.5403
	" " " *carbon exhaled*	0.5794
"	putrescent lung-tissue (mean of exp. 8, 9, and 11)	0.3819
"	fresh " (" " 12, 13, and 14)	0.3076
"	putrescent thoracic blood (mean of exp. 1, 2, 3, 4, and 5)	0.7625
"	fresh " " (mean of table)	0.0841
"	putrescent liver-tissue (exp. 6)	4.3138
"	fresh " (mean of exp. 25, 26, and 27)	0.0190

The important facts seemingly established in the above table are: the correspondence between the amount of alcohol in the thoracic blood as obtained by calculation and by experiment; that the smallest quantity of alcohol is to be obtained from fresh liver-tissue, and the greatest from putrescent liver-tissue, in which the glycogen must have undergone fermentation. The fresh thoracic blood was blood which had not traversed the lungs; the putrescent thoracic blood of course represented the same blood with all its sugar fermented.

These researches of Ford are certainly corroborated by the discovery, first made, we believe, by A. Lieben, although usually attributed to Dupré,[47] that a substance exactly resembling alcohol exists in very minute quantity in the urine even of teetotalers.* M. Béchamp,[48] apparently without a knowledge of the work of the other chemists, obtained, from the urine of persons who had not taken any alcoholic beverage for a long time, alcohol in sufficient quantity to burn it. As Lieben also found that this substance exists in the urine of dogs, horses, and lions, and as A. Rajewski[49] obtained it from healthy rabbits, it must be acknowledged that our present knowledge strongly indicates that alcohol is formed and exists in the normal organism.

If alcohol be oxidized in the body, it must of course generate force, measurable by the modern standard of the heat-unit. A little calculation will show the importance, or rather the great amount, of the generated force. According to Dupré,[50] one gramme of alcohol oxidized in the body evolves 7184 units of heat, while the same weight of lean beef gives off only 1482 units of heat. It has been estimated that 9.3 ounces of lean beef—equal to about two ounces of alcohol—will supply the necessary force to maintain the circulation and respiration of an average man for one day. That is, four ounces of strong spirit will suffice for this purpose.

In the ergographic experiments of Destrée, alcohol first (temporarily)

* It has been asserted that the substance "is not alcohol. It passes over among the earliest products of distillation, yields acetic acid on being oxidized, reduces the potassium bichromate when dilute sulphuric acid is present, and its aqueous solution has a lower density than water. It furnishes iodoform, and exists in the urine in a very small quantity." Possessing the physical and chemical characters of alcohol, to ordinary minds it is alcohol.

increased and afterwards depressed the muscle, so that the whole work done was less than the normal; but in those of Hermann Frey[51] the alcohol lessened the working power of the normal muscle, but markedly refreshed the nearly exhausted muscle. Frey believes that this increased capability of the fatigued muscle is due to the alcohol supplying an oxidizable material to the muscle which has used up its stored-up force-producing substance. Corroboration is necessary to the establishment of the allegations of Frey, especially in view of the belief of trainers that the athlete who is entered in successive events injures his chances by taking any alcohol between the two efforts.

These considerations warrant the statement that in a *certain sense alcohol is a food*,—i.e., *that it is capable of being used for the purposes of the organism*. The question how far it is able to replace fats and hydrocarbons is not at this time capable of positive answer.

The only researches which throw light upon the value of alcohol as a substitute for hydrocarbon are those which have been carried out after the plan originated by Von Noorden. According to this method the individual is brought into a condition of nitrogenous equilibrium by careful feeding, and when this condition has been thoroughly established, non-nitrogenous articles of food are withdrawn and alcohol substituted in isodynamic quantity. Under such circumstances, if the alcohol be superior to the hydrocarbon in replacing the nitrogenous material, less nitrogen should be eliminated than before its administration; if the power of the alcohol be less than that of the hydrocarbon, more nitrogen would be thrown off; if the alcohol just replaced the hydrocarbon, the nitrogenous equilibrium would not be disturbed.

Stammreich's[52] experiments upon himself were two in number. In the first experiment there was a distinct lessening of the elimination of nitrogen during the alcohol period, showing that the alcohol replaced the nitrogenous material more actively than the corresponding fat mass for which it had been substituted. In the second experiment, with a lessened amount of nitrogen in the food, there was at first no pronounced change in the nitrogenous elimination, followed, however, after two days by a marked increase, which continued for three days after the withdrawal of the alcohol. A third set of experiments were made with very little nitrogen in the food. Under these circumstances there was a great increase of the elimination of nitrogen during the alcohol period.

As the result of the comparison of these various experiments Von Noorden reached the conclusion that when the food is rich in albuminous compounds, alcohol is able to replace hydrocarbon or fats; but when the food is poor in albumin, it cannot do so. A similar series of experiments have been made by K. Miura.[53] In the experiments—in which food with but little nitrogen was given—the results obtained by Miura were similar to those of Stammreich. On the other hand, in opposition to Stammreich, Miura found that when the food is rich in albuminous material, alcohol is not able to replace the non-nitrogenous foods. Miura believes that these differences depend in part upon the facts that in Stammreich's experiments the alcohol was substituted for fats, whilst in his experiments it replaced hydrocarbons, which, according to Voit, have greater power of sparing the nitrogen materials than have the fats; so that alcohol might be equivalent to fats and yet not to hydrocarbons. How this may be must at present be left for the determination of future chemists.

All the enormous amount of labor whose results have been epitomized in the last few pages has not led to distinct positive conclusions which can be considered established beyond all peradventure; but cer-

tainly enough has been done to show that when the narcotic and stimulating influences of alcohol upon various portions of the human system are considered, its value as a food in health sinks into insignificance. For a person in health it must be considered as one of the most wasteful, uncertain, and often deleterious of known substances which are considered foods. In disease, however, when its stimulating and narcotic purposes favor its usefulness, its capability of being rapidly burnt up without undergoing any primary assimilation, and of thus yielding force to an exhausted system, may well make it an invaluable assistant to the physician. The fact, clinically well known, that in disease the human system will burn up much more alcohol than in health, indicates that as a force-giver the human system under the circumstances mentioned finds it of peculiar value.

Digestion.—The researches of W. Buchner,[54] of R. H. Chittenden and L. B. Mendel,[55] and of William Roberts are so conclusive and concordant that, so far as artificial digestion is concerned, our knowledge may be deemed positive. These laboratory results are as follows. Salivary digestion is not very actively affected by the presence of pure alcohol ; indeed, when there is not more than four or five per cent. the digestive power of ptyalin seems to be increased : ten per cent. of absolute alcohol (*i.e.*, twenty per cent. of proof-spirit) retards it slowly. On the other hand, wines and malt liquors very greatly hamper salivary digestion almost in exact proportion to their degree of acidity. Pure alcohol seems to increase rather than diminish gastric juice digestion until the amount rises to two or three per cent. ; less than ten per cent. appears not to be constantly and demonstrably inhibitive ; after twenty per cent. the digestive action may be reduced to one-third. A very important fact is that the retardation produced by a given percentage of alcohol varies greatly with the activity of the ferment and the nature of the material to be digested. Chittenden and Mendel have found that three per cent. of alcohol distinctly retards the proteolytic action of the pancreatic juice, whilst, according to A. Dastre,[56] fifteen per cent. puts an end to the artificial pancreatic digestion of nitrogenous materials.

In applying these tests of the action of alcohol upon various digestive ferments outside of the body, it must be remembered that alcohol may have a tendency to check the action of digestive ferments, and yet in the living animal, by increasing peristaltic activity or by provoking secretion, increase the activity of digestion. Chittenden, Mendel, and Jackson[57] find that alcohol temporarily increases the flow of saliva reflexly by its irritant influence upon the mucous membranes of the mouth ; and that it increases the secretion of gastric juice very greatly, the action on the stomach being exerted not only by alcoholic fluids in the stomach but by absorbed alcohol. They further determined that the ordinary alcoholic drinks agree in stimulating gastric secretion, and that the gastric juice secreted was stronger in hydrochloric acid and in proteolytic power than normal. It should be noted, moreover, that in numerous experiments

with healthy dogs with gastric fistulas, using proteid test-meals, digestion was never retarded nor accelerated, leading to the conclusion that in those cases there was a practical balance between the two antagonistic actions of alcohol upon the digestion.

Science in no way contradicts the experience of every *bon vivant* that the small doses of alcohol increase and larger amounts interfere with the activity of digestion.

SUMMARY.—Alcohol in small doses acts as a stimulant to the ganglionic cells of the cerebrum, and perhaps also to the motor tract of the spinal cord. In large amount it certainly is a depressant to the cerebral and spinal ganglionic cells, as well as the nerve-trunks. The action of small doses upon the respiratory centres is not thoroughly established, but is probably stimulant; large doses depress the respiratory centres, and finally may cause death by centric paralytic asphyxia. Upon the heart the small dose of alcohol acts as a direct stimulant, the large dose as a depressant or paralyzant. The influence of minute doses upon the vaso-motor system is not thoroughly worked out, but there appears to be a widening of the blood-paths at a time when the heart is still stimulated, so that there is a marked quickening of the blood-movement. The toxic dose of alcohol paralyzes the blood-vessels, probably both centrally and peripherally. The peripheral temperature is often increased by small amounts of alcohol, and there may be even a slight increase in the central temperature, probably caused by quickening of the circulation; the large dose of alcohol lowers the animal temperature, probably by causing vaso-motor paralysis, and thereby increasing heat-dissipation.

In regard to the effect of alcohol upon the nutrition there is much contradictory evidence, but the present probabilities are that the drug has no specific influence upon the production of heat or of carbonic acid, or upon nitrogenous elimination, and that therefore it has little or no direct effect upon the nutrition, unless it be in poisonous doses, when it certainly disturbs all nutritive processes. After absorption into the blood, alcohol is in part eliminated through the lungs, the skin, and the kidneys unchanged, but is largely burnt up in the system, probably yielding force for the working needs of the organism. Whether as a food it is in health of as much or more value than other hydrocarbons is not at present positively known.

THERAPEUTICS.—Our knowledge of the physiological properties of alcohol shows that its chief therapeutic value in acute disease is as a stimulant, a temporary imparter of power which will enable the system to stand some strain of like duration,—to bridge over some period of weakness.

The cases to which it is especially adapted may be divided into three classes :

First. Those in which there is a temporary loss of heart-power, as in fainting from exhaustion, loss of blood, or other cause. In these cases the alcoholic stimulant should, if possible, be given hot, and not much diluted ; with it should also be exhibited some more rapidly acting diffusible stimulant, such as ammonia.

Second. Those acute diseases in which the powers of the system are in danger of being used up ; to aid in the digestion of food and in the maintenance of power. Alcohol, as has already been stated, is to a certain extent a food, but it will not of itself sustain life for a long time, and should in adynamic disease always, unless for special reasons, be combined with milk, or occasionally with eggs. One great source of its value in these diseases is the power it imparts of assimilating food, and in milk punch are furnished the stimulant to digestion and the most perfect food known for digestion. This use of alcohol is apart from its office in the lowest stage of fever as a heart- and nerve-stimulant. Employed for this purpose it is useful in *all* stages of the *adynamic fevers*, such as *typhus* and *typhoid*.* By the exhibition of three or four ounces of milk every two hours, with one or two drachms of brandy or whiskey, from the beginning of the attack, in many cases the development of the severe adynamic symptoms may be prevented.

In the advanced stages of *pneumonia*, *pyæmia*, *exanthematous fever*, and other acute diseases, when the *typhoid state* is well developed, alcohol should be given boldly, to quiet by stimulation the nervous and circulatory systems, to afford a food which will in a measure replace the natural pabulum, to aid in the digestion of milk and other simple nourishment, to aid in lowering temperature : in a word, to enable the system to stand the drain upon its vital powers, and at the same time to check such drain.

Properly administered, alcohol always promotes, not arrests, secretion in these cases. The guide to the amount given should be the effects produced : so long as the drug lowers temperature and pulse-rate, moistens the dry tongue and skin, and quiets the nervous disturbance, it does good ; if, however, the tongue grows drier, the pulse puts on an angry, bounding character, and the patient becomes restless and uneasy, stimulation is being pushed too far, and the amount exhibited should be lessened. Whenever the *odor* of liquor *appears upon the breath*, the patient is almost certainly *taking too much.*

The antipyretic action of alcohol has suggested its use in cases of high temperature ; as, however, this is only one of its actions, and is not decided unless very large doses be given, alcohol cannot be employed as a general febrifuge. True arterial excitement and sthenic inflammation certainly contra-indicate its use. The rule may be laid down as follows : high temperature is an indication for the use of alcohol only when other symptoms also demand it ; in itself high temperature is never a contra-indication to alcohol. In *acute sthenic diseases*, after the progressive stage has passed and the results of the disease simply remain to be overcome, alcohol and milk will often save life. Thus, in *acute pneumonia*, when so much consolidation has occurred as to render it

* The statement of J. H. Kellogg (*Journ. Amer. Med. Assoc.*, 1895, xxv.), that the administration of brandy markedly lessens the toxicity of the urine in typhoid fever, suggests a very important line of research.

doubtful whether the exuded matter can be removed, or in *abscess*, when large amounts of pus have formed, the demand may be urgent for alcohol as a food and as an aider of digestion, and sometimes as a stimulant.

Third. Those cases in which there is a depressing agent present. In many forms of *poisoning* alcohol may be used with signal advantage simply as an arterial and nervous stimulant, to overcome the influence of a depressing agent. Thus, when death is threatened from cardiac failure in poisoning by *toxines*, *venom*, *veratrum viride*, *aconite*, or similarly acting toxic agents, whether of animal or of vegetable origin, alcohol is an important remedy, unless the poison, as in the case of an anæsthetic, is physiologically so closely allied to alcohol that the small dose of alcohol becomes a reinforcing depressant. In acute depression threatening a fatal issue it should be administered freely, not much diluted, and, if convenient, hot. From one to four ounces of whiskey should be given, repeated every ten or fifteen minutes, until slight intoxication, convalescence, or death has resulted.

What has been said up to this point in regard to the therapeutic action of alcohol has had reference to acute disease. The value of the drug in some chronic diseases cannot be doubted ; but in prescribing it the physician should never lose sight of the possible danger of producing a habit far worse in its fruits than is death itself.

In *chronic neuralgia*, in *hypochondriasis*, and in *melancholia* temporary relief may sometimes be obtained by the use of stimulants ; but the very relief afforded doubles the temptation to the frequent use of the alcohol, and, as the system becomes habituated to its action and the dose has to be more and more increased, the habit of frequent stimulation grows almost of necessity into drunkenness. For this reason we do not think that the physician is ever justified in prescribing alcohol for its narcotic stimulant effect in these cases. The chief legitimate uses of alcohol in chronic diseases are to aid in digestion, to furnish a food which, without any digestive effort upon the part of the system, shall be absorbed and shall take the place of more ordinary food, and to check excessive tissue-waste. Of course these indications exist only in such diseases as are either dependent upon or closely associated with a condition of the system in which the general nutrition is depraved. In purely local affections the use of alcohol is rarely called for except in the last moments of life, when it may always be employed to afford relief and to protract for a short time the struggle. In *chronic dyspepsia*, alcohol administered with the food often aids very materially in the assimilation of the latter ; but care should be exercised in prescribing it, for the same reasons as were given a moment since when speaking of the use of stimulants in melancholia. In many cases of *chronic neuralgia*, not as a narcotic stimulant, but as a food and a stimulant to nutrition, alcohol is often of service. The danger of establishing a fatal habit in this disease is, however, excessive. In almost all cases in which alcohol is called for in neuralgia, cod-liver oil is

also indicated, and it is generally best to exhibit the two remedies together, so as to obtain the easy assimilation of the oil and to guard against evil moral results.

In *phthisis* and its congener *scrofulosis*, there can be no doubt as to the great value of alcohol ; and in the latter stages of consumption its judicious use as an antipyretic narcotic stimulant to lessen the sufferings of the patient is perfectly justifiable. During the earlier chronic movements of the affection, alcohol taken with cod-liver oil, or in small amounts with the food at meal-times, conduces not so much to the comfort as to the well-being and recovery of the patient.

The question as to the propriety of the daily use of alcohol by healthy men is at present a very serious one, involving so many moral and politico-moral issues that it cannot be fully discussed here. Suffice it to state, as obvious inferences from our present knowledge of the physiological action of alcohol, that the habitual use of moderate amounts of alcohol does not directly and of necessity do harm ; that to a certain extent it is capable of replacing ordinary food, so that if the latter be scanty, or even if it be coarse and not easily digested, alcohol, in some form or other, is of great advantage ; that in all cases it should be taken well diluted, so as not to irritate the stomach ; and that wine or malt liquors are certainly preferable to spirits. When, as is almost universally the case in the United States, food is habitually taken in larger quantity than is required for the system, then the habitual use of alcohol distinctly is injurious, increasing the probabilities of plethora and lithæmia. The experience of Arctic explorers has clearly shown that alcohol has no heat-producing power, so that at a time when it was believed by physiologists to have such influence the Northern navigators had learned that the free use of spirits, far from enabling a man to withstand habitual exposure to intense cold, very materially lessened his power of resistance. On the other hand, the experience of almost every trout-fisherman or sportsman has satisfied him that spirits do have power to prevent "catching cold" under sudden and unaccustomed exposure to wet and cold, and that benumbed extremities will become warm and have their proper feelings return under the influence of a glass of whiskey. There is, however, nothing strange or contradictory in these experiences, and they are both in strict accord with our present knowledge of the physiological action of the drug. As is often the case, the facts were practically made out, however, before science could solve the apparent paradox. It has been abundantly shown that alcohol has no heating power ; but the chill of sudden exposure, the suffering benumbed extremities, the bronchitis that perhaps follows, all mean simply this : that, as a result of the cold, the blood leaves the surface and the extremities, the circulation fails in the outposts, and, as a consequence, suppressed perspiration—*i.e.*, suspended function of the skin—and internal congestions follow. The relief afforded by the spirits, as well as the prevention of sickness, is due simply to the power of the

remedy in maintaining the circulation and keeping the external surfaces warmed by the constantly renewed currents of fresh blood from the interior of the body.

As an *antiseptic* alcohol is sufficiently active to be useful on occasion as a dressing for wounds. Lint soaked and kept constantly wet with spirits may be applied.

ADMINISTRATION.—Almost enough has been already said upon this point, but a few further remarks seem appropriate. When stimulants are used to sustain the sinking powers in poisoning or in disease, the amount given should be almost solely regulated by the effects. Thus, in snake-bite it may be necessary to give a pint of whiskey in the course of an hour ; and in low fevers we have seen the greatest benefit result, and life apparently saved, by the exhibition of a quart of spirits a day. In snake-poisoning, one, two, three, or four ounces, as the case may seem to need, should be exhibited every ten minutes until some effect is produced or matters become hopeless. In low fevers half an ounce to an ounce should be given every one, two, or three hours, *pro re nata*, the practitioner watching the results.

The question of choice, of course, comes up in every case as to which of the spirits shall be used. We have never been able to perceive any distinct differences in their action (gin, of course, being excepted), save only that sometimes one spirit agrees better with the stomach than another. This has seemed to us to depend simply upon the personal likings of the patient, to which, therefore, the choice may well be left. In sudden collapse, some of the wines with a very high *bouquet* are believed to be more stimulating, on account of the ethers which they contain. In convalescence, and for habitual use in health, wines are preferable to spirits,—more agreeable, more tonic, and less apt to lead to excessive indulgence.

When a mild stimulant is wanted in the beginning of fevers, especially if milk punch seems too "heavy," *wine whey* may sometimes be used with advantage. It is made by pouring a half-pint of sherry or madeira into a pint of boiling milk, stirring thoroughly, and, after coagulation has occurred, straining off the whey, which may or may not be sweetened, according to the taste of the patient. *Mulled wine* is often very grateful to patients as a change. It is made by beating an egg up thoroughly with three fluidounces of sherry and adding a like quantity of water, which must be actually boiling when poured in. *Champagne* is useful in patients with delicate stomachs, especially if nausea or vomiting actually exists, and also may be employed with advantage in sudden failure of the vital powers, especially in elderly persons. It must always be very "dry,"—*i.e.*, as free as possible from sugar.

Milk punch is prepared by adding from a dessertspoonful to a fluidounce of brandy, whiskey, or rum, according to the degree of stimulation required and the taste of the patient, to three fluidounces of milk, with sugar and nutmeg to taste. The addition of a tablespoonful of

lime-water is not recognized by the palate, and renders the beverage more acceptable to the stomach when the latter is weak.

Eggnog is still more nutritious than milk punch, but is "heavier," and is usually rejected by the stomach if given too freely. It is made by beating up thoroughly the yolk of an egg with five fluidounces of milk and half a fluidounce to one fluidounce of spirits (and half a fluidounce of lime-water if required), and adding a sufficiency of sugar, with finally the white of the egg previously thoroughly beaten into a froth.

TOXICOLOGY.—The acute form of alcoholic poisoning in its minor degrees is, unfortunately, an hourly occurrence almost in every village, but that fatal results are not absolutely so rare as is generally believed is shown by the fact mentioned by Taylor, that in four years (1863–67) thirty-five deaths from this source occurred in England and Wales. It is worthy of note that in some fatal cases convulsions have preceded death.[58] The absolute diagnosis of acute alcoholic poisoning when the patient is simply seen in the advanced stage of deep coma cannot be made out. The odor of liquor upon the breath or about the person is simply a proof that the subject has been drinking, not that the symptoms are caused by alcohol. The manifestations are merely those of profound compression or congestion of the brain, of apoplexy, of opium-poisoning; and a man whose breath and urine are loaded with alcohol may have been struck down with apoplexy or poisoned with opium. Whenever in drunkenness no answer is obtainable by shaking or hallooing at the subject, the existence of apoplexy should be strongly suspected, and a very careful examination made to detect facial or other palsy; even if this be not found, judgment should be suspended.

The treatment is very similar to that of opium-poisoning, except that in many instances care should be taken to maintain the bodily temperature. The stomach should be evacuated, the patient aroused by mechanical means, strychnine and digitalis given hypodermically, the hot bath employed if necessary, and, finally, if symptoms come to the extreme, long-continued artificial respiration (Sylvester or forced) should be practised. After death, congestion of the stomach, often with ecchymosis, is the only at all characteristic lesion.

The results of chronic alcoholic poisoning, by their frequency and importance, have come practically to rank among diseases, and are discussed in treatises upon the practice of medicine, to which the reader is referred.

DIGITALIS. U.S.

The leaves of the Digitalis purpurea,* or foxglove, of the second year's growth. These are large leaves, of a dull pale green, with whitish down

* The question whether other species of Digitalis have the therapeutic properties of D. purpurea is of great interest. H. Goldenberg (*Inaug. Diss.*, Dorpat, 1892) states as the results of his experiments that D. nervosa, Stend., D. gigantea, Fisch., D. eriostachys, Linn., D. fontanesii, Stend., and D. glandulosa all possess more or less of the physiological properties of the official species, whilst D. ferruginea, Linn., is ten times as powerful as the official drug.

underneath, and have a bitter nauseous taste and a faint narcotic odor. Digitalis yields both to water and to alcohol.

Concerning the active principle of digitalis there is much confusion. In the first place it seems practically certain that there are several active principles, some of them closely allied in their physiological action as well as their chemical relations, each probably representing to a greater or less extent the pharmacological properties of digitalis. The complication arising from the difficulty of the chemical recognition of these substances has been greatly increased by the improper use of the word "digitalin." There are at least four different substances on the market to-day known as digitalin, only one of which is probably a pure ultimate principle. It is impossible here to review in detail the vast amount of contradictory work which has been done on the subject, and we will give only what seems to us the most probable relations of these drugs, with a key to the literature of their chemistry.*

There are in the leaves of digitalis the following ultimate active principles: *digitalinum verum* of Kiliani, *digitalein*, *digitoxin*, and *digitonin*. These are probably all glucosides, although there is still some dispute about digitoxin.

The first to separate a crystalline principle from digitalis was Nativelle,[1] who received the Grand Prize of Orfila in 1871. This principle is the "digitaline crystalisée," of the French Codex, and seems to be a more or less impure form of digitoxin of the Germans. "Digitaline amorphe" of the French, known as Homolle's digitalin, is probably a less pure preparation of the same principle.

By the term digitalin, as used in this country, is commonly meant the German digitalin. According to the catalogue of E. Merck, this is a mixture of digitalein, digitalin of Kiliani, digitonin, and certain inactive principles. It has been asserted that digitoxin is the chief active principle of German digitalin, but the fact that digitoxin is insoluble, while German digitalin is soluble in water, makes the truth of this assertion very improbable. It is probable that digitalein, digitoxin, and digitalinum verum of Kiliani have similar physiological powers. Arnold and Wood[2] were unable to detect any qualitative difference between the action of digitoxin, German digitalin, or tincture of digitalis. On the other hand, it seems to be proved that digitonin belongs to the saponin group of drugs, and is physiologically antagonistic to the other active principles of digitalis.

PHYSIOLOGICAL ACTION.—*Local Action.*—Locally, digitalis is probably a feeble irritant, although there is some reason for believing that the gastric disturbance which is apt to follow the administration of the drug in full doses, and which sometimes interferes greatly with its usefulness, is at least in part of centric origin.

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* Bardet (*Bull. et Mém. Soc. de Thérap.*, 1889, xvi. 253), Brouardel (*Bull. Acad. Méd.*, Paris, 1886, 2 s., xv. 528), Gubler (*Ibid.*, 1872, 2 s., i.), Nativelle (*Ibid.*, 1871, xxxvi.), Schmiedeberg (*Archiv f. Exper. Path. u. Pharm.*, iii. 19, and iv. 191), Roucher (*Gazette Méd.*, 1874), and Villejean (*Méd. Mod.*, 1890, i. 285).

Absorption and Elimination.—Digitalis yields its active principles to absorption in the intestinal tract with the greatest slowness and with some irregularity, hours usually, and sometimes days, elapsing before the full effect of the dose taken by the mouth is produced. Even when the drug is given hypodermically the slowness of its absorption renders it an unreliable remedy in emergencies. Concerning the fate of its active principles in the body we have no positive knowledge. The experiments of G. H. Roger[3] indicate that they are not destroyed in the liver, and they probably escape from the system through the kidneys.

General Action.—The first evidences of the effect of moderate doses of digitalis are an increase in the force and a slowness in the rate of the pulse, the pulse-wave becoming extremely large and hard. If the doses be increased, dicrotism develops, and increases until the pulse becomes rapid, broken, irregular, and feeble. During all this period no symptoms are ordinarily produced; after toxic doses, however, there are gastric uneasiness or vomiting, lassitude, prostration, muscular tremors, lowered reflex activity, and sometimes convulsions. (See also *Toxicology.*)

Nervous System.—Upon the cerebrum digitalis has no influence; indeed, its effects upon the nervous system are everywhere so feeble that they are not apparent except after the very largest toxic dose.

As the result of an elaborate experimental study, A. Weil[4] concludes that digitalis first lessens reflex activity by directly—*i.e.*, independently of its action on the circulation—exciting the inhibitory reflex centres of Setschenow, and after a time by directly paralyzing the spinal cord. The experiments upon which this conclusion was based are divided into two series. In the first series it was found that after small toxic doses of the poison great diminution in the reflex activity of the frog was apparent in from ten to twenty minutes, and continued until the death of the batrachian, but that this diminution for from twenty-five minutes to an hour was immediately suspended by section of the cord high up, the reflex activity returning at once to its normal state; that after large doses the reflex movements were almost abolished in five minutes, and continued so until death, but at any time during the first ten or twenty minutes they could at once be restored by section of the upper cord; and that, both after large and after small toxic doses, a time finally came when division of the cord had no power to restore the lost reflex functions. These experiments have been confirmed by Meihuizen.[5] In Weil's second series of experiments it was proved that the action of digitalis upon the inhibitory reflex centres and the cord is direct.

In these experiments the hearts of frogs were cut out, or their motion arrested by the local application of a concentrated solution of potassium nitrate, or rendered slower by a dilute solution of the same salt, and the effects of these various procedures upon the reflex activity were studied. It was found that slowing of the heart's action did excite the Setschenow's centre, but not to nearly so great an extent as did digitalis, and that minute doses of digitalis sometimes stimulated the Setschenow's ganglion and lowered reflex activity before the heart was sensibly

affected. In regard to the spinal cord it was proved that when the heart was killed by the local action of potash the reflex functions of the spinal ganglia remained intact for a much longer period than when digitalis was administered.

Muscles.—That digitalis has some influence upon the voluntary muscles has been proved by the researches of Vulpian, of Dybkowsky and Pelikan,[6] and of Gourvat,[7] all of whom have found that the muscles of frogs poisoned with digitalis respond more freely than is normal to galvanic currents. This action upon the voluntary muscles is, however, so feeble that according to Gourvat it is distinctly less than the influence exerted upon the nerves. There is some reason for believing that digitalis affects also the non-striated muscle-fibres throughout the body.

Circulation.—Although the action of digitalis upon the circulation in reptiles and mammals is very similar, there seem to be certain points of difference for which no satisfactory explanation is forthcoming.

Batrachian.—In the frog, during the first stages of digitalis action the blood-pressure is elevated and in the last stage depressed. Usually the first symptom produced is a slowing of the heart's action,* due to a prolongation of the diastole, which may be complete, but sooner or later is divided by an abortive attempt at ventricular contraction. The systole is abnormally energetic, so that the ventricles become white as the last drop of blood is squeezed out of them. As the action of the drug grows more intense, the rhythm of the heart is very much affected, the ventricle and auricle no longer beating in accord. At the same time the diastole generally becomes imperfect, one portion of the ventricle maintaining its systolic spasm, while the rest dilates. Thus, the extreme apex may remain hard and white during the diastole, and even hernial protrusions of the ventricle may occur. Finally, the heart is arrested in systole, and as the muscle so hardens all power of responding to electrical or other excitants is lost.

In some rare instances, instead of the above series of phenomena, the diastolic periods throughout are prolonged and quiet, and after several periods of relaxation, lasting for ten or twenty seconds, final diastolic arrest may occur.

It would appear definitely settled that the cardiac phenomena produced by digitalis in the frog are due in part to a direct action upon the heart itself. Boehm[8] and Dybkowsky and Pelikan have found that the slowing of the heart's beat, the increased energy of contraction, and the irregularity and final systolic arrest are produced by digitalis after division of the vagi and destruction of the spinal cord. Again, the local application of digitalis at once influences the heart (T. Lauder Brunton[9]). Moreover, R. Boehm, using the method of Ludwig and Coats, has determined that in the isolated frog's heart digitalis slows the rate of the beat but increases the expenditure of power by the heart. After a large dose

* Some observers have noted a primary acceleration of the heart's action, but this has occurred so rarely that it probably has been due to some extraneous, unnoticed cause.

this condition of cardiac stimulation is followed by a great lessening in the output of power, which is apparently due to imperfect diastole and consequent non-admission of fluid into the ventricles. The heart is still actually putting forth more power, but this power is wasted in ineffectual spasm, and does not accomplish work. The experiments of Williams[10] agree with those of Boehm in showing that the cut-out frog's heart actually exerts more than its normal force under the influence of digitalis. Williams believes that the increased work of the heart is largely dependent upon an altered tone of the muscle, producing a more complete diastolic enlargement of the ventricles.*

There seems to be no doubt that the drug increases the activity of the inhibitory ganglia in the heart. According to investigators, there is no stage in which stimulation of the vagi does not cause diastolic arrest. Indeed, Dybkowsky and Pelikan have seen galvanization of nerves produce such relaxation in the auricles after the ventricles had already become permanently contracted. Further, Boehm has found that a stimulation of the pneumogastrics which is insufficient to make itself felt before poisoning will, after the exhibition of digitalis, cause diastolic arrest lasting for many minutes.

It appears, therefore, that the peripheral cardiac inhibitory apparatus shares in the stimulant action of digitalis ; and as Boehm has found that after section of the vagi diastolic arrest never takes place in frogs poisoned with the drug, it is probable that this rare mode of death is really due to superexcitation of the inhibitory cardiac nerves.

On the other hand, however, it does not appear that the condition of inhibitory excitement is the sole cause of the slowing of the pulse, since Boehm affirms that not only are the partial contractures and the systolic arrest of the heart produced in the atropinized frog by digitalis, but also a slowing of the heart-beat.

That the systolic arrest of the frog's heart by digitalis is not of the nature of a paralysis, but of a spasm, is indicated by the fact that such drugs as muscarine, applied to the contracted heart, will cause it to recommence its beat (Schmiedeberg[11]). The experiments of François Franck[12] upon the isolated apex of the heart appear to show that digitalis acts directly upon the cardiac muscle.

According to our present knowledge, in the frog the slowing of the heart by digitalis is due partly to an action upon the peripheral vagi and partly to some other cause, whilst the increased energy of the heart is the direct result of the digitalis upon the muscle-fibre.

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* In apparent opposition to the older evidence are the researches of Donaldson and Stevens (*Journ. of Physiology*, iv.). For an elaborate discussion of this paper, see editorial in *Therap. Gaz.*, February, 1885. H. von Openchowski (*Verhandl. der Congress f. Inner. Med.*, 1889, viii.) believes that digitalis acts differently upon the right heart than upon the left, and especially upon the right and the left coronary artery, causing the latter to be overfilled, whilst the former contains no more blood than normal. We think that his evidence is not sufficient to establish a theory which in itself seems so unreasonable.

Mammal.—In the mammal the action of digitalis upon the circulation may for the purposes of description be divided into two stages. During the first stage there is marked slowing of the heart's beat, with large, full, hard pulse-waves and pronounced rise in the arterial pressure. During the second stage there is rapidity and usually irregularity of the heart's beat. In the latter part of the first stage there is marked dicrotism of the pulse, which increases during the early part of the second stage, so as to convey the impression that the increase of the pulse-rate is due to the division of the cardiac beats.

In most of the experiments of Arnold and Wood upon dogs the change from a slow to a rapid pulse has been abrupt and usually accompanied by an enormous rise of the already elevated blood-pressure. At the end the fall of pressure is very sudden and rapid, so that it has immediately preceded death.

In explaining these phenomena it will not suffice to resort to the results obtained in experiments upon the isolated frog's heart. It seems to be clearly established that in poisoning of the mammal by digitalis the heart is arrested not in systole but in diastole, since the fact has been confirmed by Donaldson and Stevens,[13] by Cushny,[14] and recently in an elaborate series of experiments made in the University of Pennsylvania Laboratory by John P. Arnold and Horatio C. Wood, Jr., the latter investigators being well informed of, and meeting Franck's denial of the diastolic arrest.*

Notwithstanding these differences, it would appear established by all the evidence that the action of digitalis upon the mammalian heart is in accord with its influence upon the batrachian heart in regard to the one great physiological fact of practical importance,—namely, that the moderate dose of the drug increases the force put out by the heart; our own experiments would indicate that this excessive cardiac energy in the mammal as well as in the batrachian may persist to the last.

The question how digitalis primarily slows and secondarily increases the pulse-rate in the mammal has been variously answered. In his original memoir, upon which has been founded our modern knowledge of the physiological action of digitalis, Traube stated that, after section of the vagi, digitalis is in warm-blooded animals, with rare exceptions, incapable of reducing the pulse-rate, and, contrariwise, that when the pulse-frequency has been reduced by the drug, section of the nerves causes an immediate and very marked rise in the rate of pulsation. Klug also affirms that section of the vagi completely does away with the slowing action of digitalis, and concludes that the lessened pulse-rate is entirely

* That there are apparent important differences in the relations of certain drugs or drug-forces to the mammalian and batrachian heart seems established, but the probabilities are that these differences are due to extraneous causes and are not essential. Thus, according to the experiments of Masi, when the frog's heart is warmed to 32° C., digitalis arrests it in diastole, and when the heart of the mouse is cooled, digitalis stops it in systole instead of diastole; whilst Donaldson and Stevens have shown that the condition of the venous circulation very materially affects the heart-action of frogs.

due to stimulation of the pneumogastric centres. The bulk of investigators, however, "such as Marme, Ackermann, Bulgari, Schnabl, Popper, and Kaufmann" (quoted from Cushny), have found that section of the pneumogastric does not completely prevent the slowing of the cardiac rate. This would seem to indicate that in the mammal digitalis stimulates centrically the inhibitory nerve of the heart, whilst at the same time also in some other way it decreases the rate of the cardiac pulsations. When to this conclusion is added the fact seemingly established by the separate researches of Ackermann, of Arthur R. Cushny, and of Arnold and Wood, that the administration of atropine entirely does away with the slowing of the pulse in the mammal, it would appear that this slowing of the pulse is due to a simultaneous stimulation of the pneumogastric centres and of the peripheral inhibitory apparatus in the heart.

It is probable that the comparative effects of digitalis upon the pneumogastric centre and periphery differ in different individuals, the centric influence usually being the most powerful, but in some cases the nerve-ending being even more susceptible to the action of the drug than is the centre; in this way the very pronounced reduction in the pulse-rate occasionally produced by digitalis in the mammal after section of the pneumogastric may be explained as due to an exceptional sensitiveness of the peripheral ganglia of the individual animals under experimentation.

In the advanced stages of digitalis-poisoning in the mammal there appears to be paralysis of the pneumogastric peripheral ending, or else such exceptional irritability of the muscle-fibres that the pneumogastric nerve has lost its control, since at this period galvanization of the pneumogastric does not perceptibly affect the cardiac action (Cushny, Arnold and Wood, and others).

Digitalis has a very marked action upon other portions of the mammalian heart than those connected with inhibition. In the first period of its action the diastole is more complete and the systoles more powerful and also thorough, so that the ventricle is more completely emptied of its blood than in the ordinary normal contraction. In advanced stages of the poisoning the movements of the heart are arhythmical, but the ventricular contractions become very rapid, and apparently do not lose their force; at least in our own experiments in the University laboratories, with the exposed mammalian heart under observation, the change from the first period of slow pulse showed itself in a rapid alteration of the systolic contractions, which become progressively faster and faster, there being at the same time a very marked increase in the arterial pressure. At the end there was a sudden and complete fall of the arterial pressure, this being simultaneous to and probably dependent upon the ventricles passing into a condition of violent imperfect fibrillary contractions similar to that which has been called *flimmerbewegung* by Kronecker.

The rhythmic action of the ventricles and auricles is not affected by

the therapeutic dose of digitalis, but after the toxic dose, at the period when the slow beat is changing into the rapid, the normal relations between the contractions of the various portions of the heart are often lost. In the last period of the poisoning the auriculo-ventricular arhythmia grows more pronounced, and finally the cardiac contractions become entirely irregular, until at last there is that condition which is sometimes spoken of as *delirium cordis*.

If the belief of Cushny, that the differences in the final result in the digitalized batrachian and mammalian hearts are because the mammalian heart is not capable of continuous systole, be correct, the only marked difference in the action of the drug upon the two hearts is in the effect upon the inhibitory apparatus.

It does not seem to us, however, that the whole matter has as yet been worked out. Neither the theories advanced by Cushny, that the arhythmia and peculiar ventricular movements of the third stage of digitalis-poisoning are the results of excessive irritability of the cardiac muscle, and that these and other cardiac phenomena in the last stage of digitalis action are produced by poisons formed in the heart itself by its own action, nor the theory that the advanced phenomena of digitalis cardiac action are largely due to excessive stimulation of the accelerators, appear to us to be established. In our experiments upon the exposed mammalian heart we have seen in the final acts of the digitalis drama happenings so curious and unexpected that at present no proposed theory as to the action of the drug is sufficient.

The question as to the comparative action of digitalis upon the ventricles and the auricles is one of distinct practical bearing, but cannot at this time be fully answered, although it is probable that the drug affects the ventricles more than it does the auricles. Kaufmann states that he has experimentally proved that the diastolic as well as the systolic intra-ventricular pressure is increased by digitalis, but that the diastolic intra-auricular pressure is slightly diminished. This would indicate stimulation of the auricles as well as of the ventricles. The pressure within the auricles would naturally not be increased, because digitalis does not increase the flow of blood from the lungs into the auricle ; on the other hand, the intra-ventricular pressure during diastole would naturally be increased by any increase in the power of the auricle.

Although digitalis does increase the muscular energy of the heart, it seems scarcely possible that the enormous rise of pressure produced by it can be owing to this alone. This *a priori* reasoning has received experimental confirmation from Malan (quoted by Fothergill), Fothergill,[15] Gourvat, and Ackermann,[16] who have found by microscopic studies that the arterioles of the frog's web, or of the mesentery of the rabbit, undergo very marked contraction, even to the partial obliteration of their lumen, after the exhibition of digitalis. Without attaching too much importance to this evidence, the finding of Traube, of Boehm, and of others, that after section of the cord high up the arterial pressure is either elevated not

at all or not nearly so much by digitalis as in the normal animal,* is a strong indication that the drug increases the arterial pressure largely by increasing the peripheral resistance without centric vaso-motor stimulation. There is, moreover, much still weightier evidence of the truth of this conclusion. J. F. Williams has also found, after reduction of blood-pressure to zero by chloral, that digitalis will cause rise of pressure. This does not, however, throw much light upon the vaso-motor action of the drug, because by enormous doses of chloral the heart is almost as much affected as is the vaso-motor system. Brunton and Meyer injected digitalin into the ear of a rabbit whose cervical sympathetic and pneumogastrics had been destroyed, but were unable to obtain any satisfactory result; there was certainly no constant perceptible contraction, although sometimes the vessels were seen to empty themselves more rapidly than before the injection. More important is the fact demonstrated by Brunton and Tunnicliffe,[17] that during an inhibitory cardiac arrest the blood-pressure sinks much less when digitalis is given than without it. Decisive are the independent, though consentaneous, researches of Ringer and Sainsbury [18] and of Donaldson and Stevens, who, using the method of Gaskell more or less modified, have apparently proved that digitalis acts upon the walls of the arterioles. They destroyed the nerve-centres of a terrapin, excised the heart, and connected bottles in such a way with the blood-vessels that liquids would run through the arteries and come out through the veins. Under such circumstances they noted a marked reduction of the rate of flow when soluble digitalin was placed in the artificial serum. That in the normal mammal under the influence of digitalis there is pronounced contraction of the blood-vessels seems also to be proved by the experiments of John C. Hemmeter, made with Ludwig's stromuhr, in which it was found that the velocity of the blood-current was markedly decreased by digitalis, though the pressure was increased. R. A. Kobert,[19] † in a series of experiments similar in principle to those of Ringer and Sainsbury, but made upon the excised kidney, found that digitalis retards

* These experiments have been contradicted by Ackermann, who states that he has many times cut the spinal cord and without exception found a very marked rise of arterial pressure follow the injection of digitalis. Unfortunately, none of these experiments have, that we are aware of, been published in detail, and it is therefore impossible to analyze or to reconcile them; but Görz (*Schmidt's Jahrbücher*, clviii.) expresses the opinion that Ackermann did not fully divide the cord in his experiments. Görz himself found that a rise is produced by digitalin after division of the cord, but of so small an amount as readily to be accounted for by the increased power of the heart. A similar rise has been observed by Kaufmann, who does not, however, give the extent of it. It is exceedingly probable that Görz's explanation is correct; moreover, it is possible that the cord in these cases was not entirely cut. We have found by actual experiment that a spinal cord may be so divided that the animal has neither sensation nor power of voluntary motion below the point of section, although sufficient nerve-fibres retain their integrity to transmit vaso-motor impulses, so that galvanization of a sensitive nerve below the point of section produces immediate rise of the arterial pressure without eliciting any pain-cries from the animal.

† Kobert tested two specimens of *digitoxin* and *digitalein* which had been supplied by Schmiedeberg, their discoverer, and found that instead of contracting the vessels of the kidney they actively dilated them and increased the flow of liquid.

greatly the flow of liquid through the organ, and therefore acts directly upon the coats of the smaller vessels; also that digitalis and the nitrites (see page 246) are mutually antagonistic. The conclusion appears to be established that digitalis *has a direct action upon the walls of the arterioles*, but it is highly probable that it *also acts upon the vaso-motor centre in the medulla.*

It has been shown that the dicrotism in the frog's pulse is due to an attempted diastole before the systolic impulse has yielded; and Kaufmann has determined that in the mammal a similar partial relaxation, arrested by a renewed very brief systole, occurs and gives origin to the double pulse. Kaufmann has also noticed that a tendency to cardiac tetanus is manifested in the horse, as in the frog, under the influence of digitalis, but that in the former animal a permanent, complete cardiac spasm never occurs.

The following proposition expresses our present knowledge, and probably is very close to the truth in regard to the action of digitalis upon the lower mammals.

Digitalis in moderate doses stimulates the muscular-motor portion of the heart (probably its contained ganglia), *increases the activity of the inhibitory apparatus*, and *causes contraction of the arterioles*, probably by an action on the vaso-motor centres in the cord, and also upon the walls of the arterioles. As a consequence of the first action, the cardiac beats become much stronger; as the result of the last, there is a narrowing of the blood-paths, and an increased resistance to the passage of the vital fluid, which, acting on the already excited inhibitory system, aids in the slowing of the pulse.*

Man.—According to our experience, decided therapeutic doses of digitalis, in man, produce great reduction of the pulse-rate and sometimes dicrotism of the pulse, and increase the size and force of the wave, at the same time augmenting the arterial tension. Poisonous doses induce, after a time, increase of the pulse-rate, with smallness of the wave.

Sphygmographic studies of the effect of digitalis upon persons suffering from various acute and chronic diseases have been made by Legroux, Bordier,[20] Constantine Paul,[21] and Paul Lorrain.[22] The problems offered by these gentlemen are so complex as to render a detailed study almost impossible; but, as a whole, their tracings seem to confirm our personal experience. Paul Lorrain calls attention to the fact that when the drug has reduced the pulse-rate very greatly a second abortive systole can, on auscultation, sometimes be heard occurring during the long dia-

* Bayet (*Acad. Royale de Méd. de Belgique*, iv. série, 1892) is stated to have found in the dog that the pressure in the pulmonary artery is depressed rather than increased under the action of digitalis and strophanthus at a time when the aortic pressure is enormously augmented. The importance of this is easily seen; it implies an extraordinary physiological disassociation between the right and left heart, and has also very close relations with the therapeutic use of the agents in pneumonia and other conditions. We have not seen any detailed report of the experiments of Bayet, nor have we seen the memoirs of Bradford and of Bockenham, who are quoted, without reference, as having obtained a different result in 1890.

stole, and some of his sphygmographic tracings are markedly dicrotic. It is evident that in man the second systolic movement occurs precisely as in animals; and it seems very certain that the proposition framed for the lower mammals applies also to man.

When the pulse has been reduced by digitalis to 40 or 50 a minute, the change from the recumbent to the erect position will not infrequently suffice to alter at once its character, so that it will become small, and rapid, even 150 per minute. The explanation of this seems to be that the heart of such a patient is just in the position in which the diastolic impulse is being overcome by the excessive systolic stimulation of the drug. While the patient is recumbent, the line is not passed over, but the additional stimulation of the erect position carries the heart beyond the limit of regular diastole, and the over-effects of the drug are at once manifested.

Urinary Secretion.—The influence of digitalis upon the urinary secretion in health has been studied by numerous observers, with such diverse results as to prove that the action of the drug on the kidneys is so inconsistent and varying as to render it probable that it is in great measure indirect rather than direct. Thus, Jörg, Hammond,[23] and Brunton have found the secretion more or less decidedly increased, and Homolle,[24] Winogradoff,[25] Stadion, and, according to Brunton, also Krahmer, Kluyskens, Vassal, and Shohl, have found it either uninfluenced or diminished. Kaufmann has found it uniformly diminished in the dog.

The urea in the apparently very careful experiments of Winogradoff, of Stadion,[26] and of Hammond was diminished, while in the almost equally elaborate experiments of Brunton it was increased. All four observers noted lessening of the chlorides. Mégerand, using the crystallized digitalin of Nativelle, found his urine increased twenty-five per cent. but his urea diminished twenty per cent. Auguste Meusnier[27] has sought without success for sugar in the urine both of patients taking large doses of digitalis and of rabbits poisoned with the drug. Kaufmann[28] states that digitalis leaves, or preparations which produce local irritation, cause in the dog an increase in the elimination of urea, but that when digitalin is given in solution the excretion of urea is diminished. G. P. Sereschnikow, as the result of experiments upon man, finds that digitalis has no pronounced constant effect upon nitrogenous elimination. He is confirmed by Alexëëvsky,[29] whilst I. Beljakow[30] asserts that the drug increases the elimination of the chlorides, sulphates, and phosphates.

Temperature.—*Toxic* doses of digitalis lower the temperature a number of degrees in healthy men and animals. It would seem, however, that the fall of temperature is generally, if not always, preceded by a rise, as has been noted by Bouley and Reynal, by Duméril, Demarquay, and Lecointe (quoted by Brunton), by Hirtz, by Legros,[31] and by Gourvat. Kaufmann believes that such rise is due to the local irritation caused by the drug, and asserts that if no irritation be produced there is

always in the animal a fall of rectal temperature (0.4–0.5° C.) after even a feeble dose of digitalin.

The effect of *therapeutic* doses in the normal condition has not been closely studied, that we are aware of. But in a number of cases, chiefly of pneumonia, Z. E. Coblentz,[32] found that about twelve hours after the fall of the pulse there was also a fall of temperature. The tendency of our present knowledge is to connect the changes in temperature induced by digitalis with the changes of the circulation ; and it seems very possible that therapeutic doses in health may be found to increase bodily heat, although in fever they may diminish it.

SUMMARY.—It would appear to follow, from experiments upon frogs, that the toxic dose of digitalis primarily inhibits reflex action by stimulation of Setschenow's centre, and subsequently directly paralyzes the motor tract of the spinal cord. This influence is not, however, very apparent, even in the lower mammals, and in the human individual the symptoms of digitalis-poisoning are chiefly manifested in irritation of the stomach and disturbance of the circulation, death finally occurring in collapse, sometimes preceded by delirium, stupor, or convulsions, though consciousness is long preserved. The therapeutic dose of digitalis acts almost solely upon the circulation, slowing the rate and increasing the force of the heart's beat by a direct stimulating action on the pneumogastric nerves and upon the heart itself. By this cardiac influence, and also by contracting the blood-vessels through a direct action upon their walls, and also probably upon the vaso-motor centres, the therapeutic dose of digitalis enormously increases arterial pressure. Probably by its direct influence upon the heart-muscle, and also by stimulating the pneumogastric or trophic cardiac nerve, and by increasing the blood-supply of the heart, in certain diseased conditions digitalis acts not only as a cardiac stimulant, but also as a cardiac tonic. In the frog the heart stops in systolic spasm ; the mammalian heart, after going into a condition of fibrillary contractions, ceases all movement in diastole. The active principles of digitalis are absorbed and probably eliminated through the kidneys, though in health the diuretic action of the drug is extremely uncertain. Upon the alimentary canal digitalis acts as an irritant, affecting the stomach more than the intestines, and often, when in full dose, producing gastric pain and vomiting.

THERAPEUTICS.—The chief clinical use of digitalis is in diseases of the heart ; and from what has been said of its physiological action it logically follows that it should be useful in loss of cardiac power.

When the muscle of the heart is for any reason unequal to the task set it, the systoles become rapid and imperfect, and by this irregular action, the ventricles neither completely filling nor completely emptying themselves, increase the embarrassment. Under these circumstances, digitalis, by lengthening the diastolic pauses and increasing the force of the systolic contractions, causes the ventricles to fill themselves completely in the one and to empty themselves completely in the other act. By subduing irregular action through the inhibitory nerves, and by energizing the muscular power of the heart-walls, the remedy is of incalculable service, and, increasing arterial tension all over the body, causes the

disappearance or lessening of symptoms due to low pressure in the arteries.

It is a logical necessity, if our reasoning as to the physiological action of digitalis has led to a correct result, that the drug should be of the greatest service when the lesion is simply loss of cardiac power ; and clinical experience tallies with this *a priori* argument. In *simple dilatation*, or in *simple failure of the cardiac muscle* without degenerative changes or valvular lesion, the results of the use of digitalis are most favorable.

On the other hand, in *simple hypertrophy* digitalis does harm, and should never be used. It must be borne in mind that although this agrees with what the experimentalist has proved to be the action of digitalis, yet it was discovered independently as a clinical fact by practitioners. Thus, Niemeyer, who ridiculed experimental therapeutics because he would not take the trouble to study them deeply and practically and was therefore incapable of understanding them,—Niemeyer says, "Digitalis in pure uncomplicated hypertrophy is unsuitable."

Valvular lesion of the heart, as is well known, gives rise under unfavorable circumstances to dilatation, but in favorable cases to hypertrophy, or rather in the great majority of cases to hypertrophy with dilatation. Following out the principles already inculcated, it might seem at first that the use of digitalis in hypertrophied hearts with valvular lesion ought to be reprobated. But it is known clinically that digitalis often does good in valvular lesion with enlargement of the heart. The results of logical deductions from our physiological conclusions as premises are, however, not really at variance with this. It must be borne in mind that structural hypertrophy and functional hypertrophy are different things : by this is meant that although a heart be enlarged and absolutely stronger than normal, yet it may be, relatively to the work required of it, *weak*. Thus, if 1 represents the normal work of the heart and 1 its normal power, if the former be increased to 4 and the latter to 3 the heart is really in the position of a weak organ, although possessed of three times its original strength. Hence it is that digitalis is often useful in valvular disease with hypertrophy. In the vast majority of cases the heart with diseased valves is in the position just spoken of ; but sometimes the work advances only to 2 and the strength to 3 ; then the hypertrophy becomes excessive, and digitalis will increase the difficulty.

In *mitral insufficiency* and in *mitral stenosis* digitalis is often of great service. It is evident that in both instances the valvular lesion leads as its first result to pulmonic hyperæmia. How does the digitalis lessen this? In the case of *stenosis*, the diastole being lengthened by the remedy, the auricle is afforded more time to empty itself into the ventricle through the narrowed orifice, and at the same time is strengthened in its contracting power ; evidently, then, the left ventricle when its systole occurs will have much more to contract on than before the digitalis was administered, and the amount of blood in the systemic circula-

tion will be increased,—*i.e.*, the amount in the pulmonic circulation will be diminished; further, the right ventricle will have greater power afforded it to force the blood through the lungs.

In *mitral insufficiency* the mechanism is different, but the result is the same. The increased power of the systole will throw proportionately more blood through the aortic orifice than through the partially open valve. The opening at the insufficient mitral valve is much smaller and more obstructed than the aortic orifice. As the force or rapidity of the current increases under the action of digitalis, the friction becomes greater at both orifices, but the ratio of increase is evidently far higher in the small choked mitral leak than in the wide aortic opening. Hence the large orifice constantly gains upon the smaller as the cardiac force is increased, and, more blood passing into the systemic circulation, the pulmonic vessels are relieved. Again, the right ventricle shares the stimulant action of the drug, and acts more strongly upon the pulmonic circulation, resisting the direct backward flow from the auricle. There are cases of mitral cardiac disease in which digitalis seems to be indicated, but when given acts unhappily. In some of these cases the augmented distress is probably caused by a strain upon the auricles. If the ventricle be already too strong for the auricle, and if by virtue of a very patulous mitral valve the backing of the blood upon the auricle is very easy, it is readily understood how increasing the power of the ventricle may augment the auricular strain. Especially is this consideration important in the light of Kaufmann's researches, which seem to show that the ventricle is more affected by digitalis than is the auricle, and hence that a stimulated ventricle may have to be met by a non-stimulated auricle.

In *aortic constriction* digitalis is useful when the heart-power begins to fail. In these cases compensatory hypertrophy, with slowness of action, is very apt to occur, or even to become excessive; much more frequently does this happen than in mitral disease. Again, in *aortic insufficiency* the prolonged diastole of digitalis action favors the return of blood to the heart, and is not advantageous. It is evident that digitalis is not so generally useful in aortic as in mitral disease: nevertheless, when the heart-muscle fails, and the hypertrophy is not compensatory, the drug is useful in both aortic stenosis and insufficiency.

From the considerations which have been brought forward, it is very evident that a knowledge of the relation of the heart-muscle to the work required of it in any individual case is much more necessary to the therapeutist than to know what valve is diseased.

In "*irritable heart*" of soldiers—a disease or condition of cardiac irritability evidently connected with muscular weakness, and very probably dependent upon exhaustion of the inhibitory nerves—Da Costa[33] found that in the early stages of the affection digitalis not only acted better than any other remedy, but even, when administered continuously for some time, often effected a permanent cure. When hypertrophy had taken place, the drug was of little use.

The relief afforded by digitalis in not too inveterate cardiac disease is often in a measure permanent, because the drug may aid very materially in the production of compensatory hypertrophy. Dilatation is certainly more apt to occur when the muscular fibre is lax and acting feebly than when it is toned up and in vigorous play ; secondly, the stimulus to action in a muscle is almost of necessity directly or indirectly a stimulus to its nutrition ; thirdly, it appears probable from the researches of Gaskell that the period of inhibition is one of structural upbuilding, and that therefore the pneumogastric nerve is trophic in its nature, so that it is probable that digitalis, by stimulating the trophic cardiac nerve, benefits the cardiac nutrition ; lastly, improved systemic circulation means in a far more intense degree improved blood-supply to the cardiac muscle, as is shown by the following considerations.

During systole the cardiac muscle contracts so as completely to squeeze out all the venous blood from the heart-walls. The arterial blood enters during diastole, and the force which drives it into the relaxed walls is derived from the arterial system. The coronary arteries arise nearly at a right angle to the aorta : the blood squirts into the latter during systole in an unbroken stream, and probably does not enter freely the coronary artery. But when the reflux wave comes, the aortic valve flaps to, and the whole pressure of the blood-column forces the liquid into the open cardiac arteries. If the arterial system be emptied, or nearly so, the arteries are not distended sufficiently to give origin to a powerful reflux wave, and but little blood enters the coronary artery,—*i.e.*, the cardiac walls. The dilated feeble heart is unable during systole thoroughly to free its walls of venous blood, and during diastole the force is lacking for driving in the arterial blood. Digitalis enables the cardiac muscle completely to free itself of venous blood, and at the same time, by restoring to a greater or less degree the normal balance of the circulation and removing the excess of blood from the general venous system, gives the aorta sufficient blood to provoke an active reflux.*

That digitalis exerts the nutrient and trophic influence here set forth has been strongly confirmed by the research of Hare and Coplin,[34] in which it was found that the continuous giving of digitalis to young pigs produced a distinct increase in the size and weight of the heart as contrasted with control animals of the same litter.

If in *aneurism*, or in general *capillary atheroma*, there be increased resistance to the circulation, and the heart have not sufficient power to

* We have let this paragraph stand as in previous editions, although the experiments of Martin seem to show that the circulation is most active in the heart's wall during systole. The appearance of the wall of a diastolic heart as contrasted with that of a systolic heart makes one, however, loath to admit the conclusion that the blood enters the muscles as freely during systole as in the first period of diastole. Moreover, even if Martin's view were adopted, the therapeutic reasoning would have to be changed in wording only, not in drift ; the facts remaining that the heart-muscle feels most powerfully failure of arterial circulation, and that therefore cardiac overwork and starvation are apt to go hand in hand, so that the relief of the circulation by the digitalis may bring about permanent nutritive changes in the heart-muscle.

meet this, digitalis may be useful, but must be employed with caution. It not only increases arterial pressure, but also causes the pulse-wave to be of enormous size as well as power, so that there is great danger of distending and tearing open the thinned wall of an aortic aneurism. The use of digitalis for the purpose of "quieting the circulation" in aneurism is very dangerous. We have seen immediately fatal hemorrhage produced thereby.

In *cardiac dropsy* digitalis is of service probably not only by regulating through the heart the circulation, and by evacuating the surplus fluid through the kidneys, but also by an action upon the vessels, vasomotor weakness being evidently a strong factor in the production of dropsy.

In *endocarditis* and in *myocarditis* with marked irregularity of the cardiac action and failing power there is naturally a strong impulse to the administration of digitalis. It should be remembered, however, that in an acute inflammation of the lining membrane of the heart the action of the heart is often really of the nature of an excitement, and that, therefore, it would *a priori* be expected that digitalis would do harm rather than good. Restrained by this belief, we have never used digitalis boldly in this condition, but from the doses given have failed to perceive any good effect. In the after-stages of an endocarditis, when the heart is troubled with recent patency of valve, digitalis is a remedy of the very greatest importance, often relieving the symptoms distinctly and very strongly favoring the development of that compensatory hypertrophy in which lies the only hope of the patient. During the exhibition of the digitalis, however, the patient should be closely watched, and any evidence of either action or growth of the heart should lead to the suspension of the drug.

In acute myocarditis digitalis is commonly absolutely inefficient. How far its action upon the muscle itself will render it harmful is at present unknown.

These statements are so correct that in cases of rapid degeneration of the muscles from diseases of the coronary artery the effect of digitalis can sometimes be made available for diagnostic purposes. When the symptoms point strongly to coronary artery diseases, and digitalis freely given fails to exert any perceptible influence upon the heart, the prognosis is most grave.

Digitalis in large doses is a valuable cardiac stimulant in *syncope* or sudden *collapse* from hemorrhage or other cause. To overcome its slowness of action we have used it hypodermically often with excellent effects. From twenty to thirty minims of the tincture should be injected into the arm, and repeated in half an hour if absolutely necessary, or a grain of digitalin may be substituted. In our experience* digitalin has several times given rise to severe local irritation, the tincture very rarely.

* Local irritation, and even the production of abscesses, have also been noted by various observers besides ourselves. See Witkowski (*Deutsches Archiv f. Klin. Med.*, xviii. 142); also Pel (*Centralb. f. Med. Wiss.*, 1877, 169).

In many cases of general debility or so-called *neurasthenia*, although there may be no disease of the organs especially concerned in the circulation, the latter is exceedingly feeble, and, as a consequence, all portions of the system are imperfectly supplied with blood. Under these circumstances preparations of digitalis are very useful as general tonics.

A number of eminent physicians assert that they have obtained excellent results by the use of half an ounce of the tincture of digitalis in the treatment of *delirium tremens*, especially in those cases in which the pulse is very soft and feeble. The evidence of the value and safety of the remedy in such cases is too strong to be overlooked, but does not indicate the possession of narcotic properties by the drug. The rest and sleep which have followed the administration have probably been the result of the cardiac stimulation and the increased flow of blood to the nerve-centres. Enormous doses of digitalis are tolerated in these cases, probably because the heart has become by long habit very much benumbed to the influence of stimulants. Their use is not, however, entirely free from danger.

Digitalis is a very important remedy in the treatment of poisoning by such substances as muscarine, delphinine, aconite, and the nitrites, which have been proved to be directly antagonistic to it in their action upon the heart.

Dobie[35] reports a case of recovery after the ingestion of an ounce of Fleming's tincture of aconite, apparently due to the hypodermic injection of twenty minims of tincture of digitalis and the exhibition by the mouth of three doses in an hour of a mixture of tincture of digitalis (one drachm each dose), brandy, and ammonia.

Digitalis is often of great value in various acute diseases,* such as *adynamic pneumonia* and *adynamic fevers*, by maintaining the heart's action. It can have no effect upon the diseases themselves, but may help most opportunely to sustain the heart during a crisis or a period of strain upon it. When in any form of *pneumonia* the right heart is yielding to the strain of forcing blood through pulmonic capillaries pressed upon and reduced in their aggregate lumen by exudation, digitalis may be of the utmost service.

With the idea that digitalis is an active *antipyretic*, it has been prescribed in various acute diseases, sometimes with asserted good results. As already stated, toxic doses of digitalis at first elevate the temperature; and proof is wanting that in healthy men therapeutic doses have any decided influence in depressing the temperature. There seems to be, therefore, no good physiological basis for the antipyretic use of digitalis; at the same time, it is very possible that it may directly or indirectly lower the temperature in disease. Clinical proof of this is, however, still wanting. The strongest evidence in favor of such action is fur-

* Consult Hankel (*British and Foreign Medico-Chirurgical Review*, xxxi. 513), Grimshaw (*Dublin Quarterly*, June, 1873), and Anstie (*London Practitioner*, Sept. 1873).

nished by the records of Wunderlich,[36] according to which from half a drachm to a drachm of digitalis, given in divided dose during three or four days in the second or third week of severe *typhoid fever*, immediately produces a slight fall of temperature in a large proportion of the cases, and sometimes a considerable fall. This fall is said not to last more than a day, when the temperature rises again, but in cases favorably affected does not regain the original height ; the pulse is very much lowered in frequency, and remains about uniform for four days. It is evident that at least in some of these cases of Wunderlich's the drug was given about the time natural defervescence would be expected to occur, and that the slight reduction of temperature brought about at such time does not argue very strongly in favor of the proposition that digitalis is a powerful antipyretic in disease. Far more extensive and complete observations must be made upon a rising, not a falling, temperature before any satisfactory conclusion can be reached. At present the antipyretic use of digitalis should be purely tentative. In *puerperal fever* Winkel[37] believes that digitalis does good by its action on the heart, by contracting the arterioles of the uterus, and by lowering temperature.

The property of causing contraction of all unstriped muscular fibres has been attributed to digitalis, but, while the probabilities are certainly such as to invite investigation, we have no definite knowledge upon the subject. Dickenson[38] asserts that it has a powerful action in causing the uterus to contract and to arrest hemorrhage,—in *menorrhagia*, a few minutes after an ounce and a half of the infusion is swallowed, severe pains resembling those of the first stage of labor coming on, with a momentary profuse discharge of blood and clots, if there be any present, followed by arrest of the flow for hours. Stadion[39] states that digitalis is capable of temporarily but completely annulling the activity of the sexual organs, and that it may be regarded as a true anaphrodisiac. M. Gaunot[40] makes the same assertion, and advises the use of the drug in *spermatorrhœa*.

The use of digitalis as a diuretic will be considered under that heading.

Toxicology.—In poisoning by digitalis, the first symptom of any severity is generally vomiting of mucus and bile, very violent and very often repeated. At the same time a feeling of heat of the head, disordered vision, and vertigo manifest themselves. The pulse at this time in the horizontal position may be full and strong and slow, but on the patient's rising becomes weak and rapid. The face is pale. The vomiting continuing, profound prostration comes on, and the pulse becomes feeble, small, and irregular, although the beat of the heart may be strong and hard. The eyes are very prominent, the pupils fixed and dilated : * according to

* Hauber (*Münch. Med. Wochensch.*, 1890) details a case of death, due, according to his belief, to digitalis-poisoning, with contraction of the pupils.

Tardieu, an almost diagnostic symptom is the blue color of the sclerotic. Abundant salivation sometimes occurs. Intense headache and pains in the back or limbs are often complained of. Diarrhœa is very generally present; the urine may be suppressed. The intelligence is often perfect in the midst of profound collapse, but delirium more or less violent finally comes on. Death, usually preceded by stupor or by convulsions, takes place most frequently in one or two days, but has occurred as late as the tenth day and as early as three-quarters of an hour.*

In the majority of cases of digitalis-poisoning the patient recovers. When this happens, the symptoms gradually ameliorate. Cardiac weakness, and even a *bruit de souffle*, with more or less exophthalmos,† is said to have persisted for weeks in some cases. In poisoning by digitalin the symptoms are those of rapid digitalis-poisoning,—violent vomiting, intense cephalalgia, and sometimes rachialgia, irregular, feeble, intermittent pulse, and paroxysms of suffocation.

The minimum fatal dose of digitalis is not known. A large teaspoonful of the tincture is said to have caused alarming symptoms in a young puerperal woman (Tardieu,[41] Obs. VIII.); twenty grains of the extract proved fatal on the tenth day (Tardieu, Obs. VI.), and two and a half grammes of the leaves in infusion on the fifth day (Tardieu, Obs. X.); fifty granules (one-fiftieth of a grain each?) of digitalin have been recovered from (Tardieu, Obs. XII., XIV.); about one-fourth of a grain of digitalin[42] produced very violent but not lethal symptoms. In the only fatal case of digitalin-poisoning we know of (*Affaire Couty de la Pomerrais*), the amount ingested was unknown.

The treatment—after the evacuation of the stomach and bowels, and the very free administration of tannic acid, as the best, although an unreliable, chemical antidote—should consist in the exhibition of opium and of alcoholic stimulants, with rest in the horizontal position. We know of no recorded experiences with the antagonistic poisons to digitalis, such as aconite or muscarine. As it is possible that while so far as the heart is concerned they may be really antagonistic and yet may intensify the action of digitalis on the cord, their use requires caution.

Two cases, one ending fatally, of what may be considered *chronic digitalis-poisoning* have been reported by Köhnhorn.[43] The symptoms were loss of appetite, tinnitus aurium, vertigo, lowering of the rate and force of the pulse, diarrhœa, weakness, general anæmia, and syncopal attacks. The only lesion found at the autopsy was congestion with ecchymosis of the gastro-intestinal mucous membrane.

* See case reported by M. Barth (quoted by Tardieu). In a case of poisoning by ten grammes of tincture of digitalis, said to contain twenty milligrammes of digitalin, the symptoms were vomiting, great pain in the head, prostration, a very small pulse,—40 per minute,—anuria, and a systolic bruit heard over the whole heart, having its maximum intensity at the base. Recovery occurred in two days (*Mém. Soc. de Méd. de Bordeaux*, 1884, 397).

† As was first noticed by Lauder Brunton, in dogs poisoned with digitalis a blowing systolic murmur may be at times heard, due to an irregular action of the papillary muscles.

ADMINISTRATION.—Digitalis may be given in substance in the form of pills; the dose being one grain three times a day, increased until some effect is produced. The solid extract (EXTRACTUM DIGITALIS, U.S.) is less reliable than the leaves; its dose is one-fifth of a grain (0.016 Gm.). When a rapid action is desired, one of the following official preparations, or the digitalin, should be used: INFUSUM DIGITALIS (1.5 per cent.),—dose, one fluidrachm to half a fluidounce (3.75–15 C.c.); TINCTURA DIGITALIS (fifteen per cent.),—dose, five to twenty minims (0.3–1.2 C.c.); EXTRACTUM DIGITALIS FLUIDUM,—dose, one to two minims (0.06–0.12 C.c.).

In emergencies where single doses are administered they may be very much larger than those here given. Thus, of the tincture, two fluidrachms or even half an ounce may be exhibited; of the infusion, a wineglassful. Moreover, in desperate cases, the physician is justified in taking the risk of the administration of repeated very large doses of digitalis. We have seen a number of cases of excessively severe chronic cardiac failure, with Cheyne-Stokes respiration, orthopnœa, and almost absolute insomnia, in which the administration of half a drachm or a drachm of the tincture of digitalis three or four times a day has enabled the patient to resume for a time the ordinary duties of life. In almost every case of this character which we have watched, death has finally come by sudden syncope, while the patient was still going about and enjoying a comfortable life. We do not believe that the arrest of the cardiac action has been due to a direct action of the drug, but to the fact that the enormous doses have stimulated the heart and steadied its expenditure of force, so that it was enabled to go on until the last particle of cardiac vital power was exhausted. H. C. Wood further says that in an experience of thirty-five years in which he has used digitalis, frequently in enormous doses, he has seen but one case in which he thought it did serious harm by a toxic action. The infusion of digitalis is believed by many practitioners to be more active than the tincture. This is simply because the infusion is commonly used in much larger doses than the tincture. Either preparation is efficient if properly made from fresh leaves.

When digitalis is administered persistently, its first evident influence may be suddenly developed after long delay.[4] It is said that sometimes the first marked symptom of this so-called "*cumulative action*" is severe syncope, followed by paraplegia, vomiting, diarrhœa, delirium, general insensibility, and death. Such cases must be extremely rare: usually a sudden drop of the pulse is the most serious effect, provided that the *administration of the remedy be at once suspended.* It is a matter of much importance to determine when this cumulative action is to be expected. It is probably connected with slow absorption and elimination, and is much more prone to occur when there is no diuretic effect. It is also very apt to appear after tapping: the sudden removal of pressure from the vessels leads to the picking up from the tissues of serum,—saturated,

it may be, with digitalis principles,—and also to the rapid absorption of any digitalis which may be in the alimentary canal. T. Lauder Brunton and J. Theodore Cash [45] find that high temperature so affects the cardiac inhibitory apparatus in the cat that it will not respond to digitalis, and believe that high temperature greatly interferes with the action of digitalis. In this they are abundantly sustained by general clinical experience ; very commonly in high fever it seems almost impossible to obtain the digitalis pulse. In *pneumonia* and other diseases with high temperature and a sudden defervescence some care should be exercised in the very bold use of the remedy, lest when the temperature suddenly falls inordinate digitalis effects may appear. Fear of the cumulative action of digitalis should not interfere with its persistent administration in cases of cardiac or other disease in which it is indicated, but should lead the practitioner to interrupt its use at intervals so as to allow the clearance of the system.

If a representative of digitalis in small bulk is desired, probably the best preparation is Merck's German *digitalin*. It has commonly been deemed uncertain, but, according to the clinical reports of Beates [46] and the experiments of Arnold and Wood, this is because it has been habitually given in absurdly small dose. According to the closely agreeing results of these investigators, one-quarter of a grain (0.015 Gm.) is about equivalent to fifteen minims of the tincture, and represents the full therapeutic value of digitalis. The dose was formerly considered one-fiftieth to one-thirtieth of a grain (0.0013–0.002 Gm.). It seems to be, however, equally as irritant as the tincture, and offers no distinct advantage except its small bulk.

Digitoxin, although powerful enough, seems, on account of its insolubility and irritant properties, not to be generally useful. The dose may be given as one-two-hundredth to one-one-hundredth of a grain (0.0006–0.0003 Gm.). The dose of Nativelle's digitalin is said to be one-one-hundredth to one-sixtieth of a grain (0.0006–0.001 Gm.).

STROPHANTHUS.

Under the names of Kombé, Inèe, Onaye, Pahouius poison, there have reached Europe various African arrow-poisons, which are now believed to be derived from one or more species of the tropical genus Strophanthus,—apocynaceous climbing shrubs. The name of Strophanthus Kombé was given by Sir John Kirk to the tree which he first identified as the source of the Kombé poison ; but botanists are at present agreed that the species is the Strophanthus hispidus of De Candolle. Langgaard states that there are eighteen species of the genus, and that the pods of at least two have entered commerce. The seeds within the pod are abundantly provided with very long, deciduous hairs, which are apt to be shed within the pod itself, and are so numerous as to weigh nearly as much as the seeds. They contain an intensely bitter crystalline principle, *strophanthin*, which is partly soluble in water, and has been shown by T. R.

Fraser to be a glucoside, convertible by sulphuric acid into glucose and crystalline *strophanthidin.*

Local Action.—Locally, strophanthus and strophanthin are exceedingly irritant to mucous membranes. Strophanthin is also an anæsthetic, M. E. Gley[1] having found that one-thousandth of a grain of strophanthin caused in the rabbit's eye not only a pronounced myosis but a very rapid and durable anæsthesia. It is true that Steinbaugh concluded that this anæsthetic action is not due to strophanthin but to some other constituent of strophanthus, but Hare and De Schweinitz have found that in this there was some mistake, and that strophanthin itself is powerfully anæsthetic, but is so irritant that its application to the eye may be followed by inflammation or even ulceration.

Absorption and Elimination.—Strophanthus yields its active principle readily to absorption and elimination. It is therefore a promptly acting drug, but has sufficient permanency for the effects of a single dose to last some hours. Elimination is, however, probably too free for any cumulative effect like that of digitalis, since no certain cases of such action appear to be on record.

General Action.—In the healthy man strophanthus in sufficient dose produces fall in the rate of the pulse, with increase of force, without alteration of the respiration, but, if the dose has been large enough, with some gastric irritation and, according to Drasche, a slight fall of temperature. In Drasche's experiments the hypodermic injection of fifteen drops of the tincture induced violent local irritation, repeated vomiting with nausea, pronounced diuresis, and a fall of the pulse. Twenty drops given by the mouth decreased the pulse thirty beats.

In the lower animals strophanthus produces symptoms similar to those that it causes in man, the diarrhœa often being especially violent. No cases of human poisoning have been reported, but after fatal poisoning in the lower animals, evidences of irritation in the gastro-intestinal tract are usually present, and violent irritation and even inflammation of the secreting structure of the kidneys, with small hemorrhages, have been noted by several observers. Mairet and Combemale also state that the blood-globules are frequently altered, and the urine, before death, albuminous. The absence of nervous symptoms until very late in the poisoning shows how very little influence strophanthus has upon the nervous centres. An observation upon the lower animals made by Mayeur[2] and by Lemoine[3] is of great practical interest, especially since similar results have been obtained by some of the German authorities in man. These observers found that strophanthus has a tendency to accumulate in the normal system, so that when small doses are given daily for a length of time, after a time violent and even fatal poisoning results.

The first to make elaborate experiments with strophanthus was T. R. Fraser.[4] One-twentieth of a grain of the extract of the seeds produced in the frog stiffness of the limbs and gradual loss of reflexes and of voluntary movement, the respiration continuing after the cessation of the heart's beat.

Nervous System.—Upon the general nervous system strophanthus appears to have little or no action. It is true that Bahadhurji[5] states that preceding the paralysis there is a stage of hyperæsthesia, and that

the motor nerve-trunks are affected by the drug, but these affirmations have not, that we are aware of, been confirmed.

Muscles.—The chief physiological influence of strophanthus is as a muscle-poison. In Fraser's experiments, the muscles of a leg being protected from the poisoning by tying the arteries, galvanization of the nerve caused active contractions at a time when muscles elsewhere failed to respond to any irritation of their nerves or substance. The first influence of the poison upon the muscular fibre is to increase its tonicity, and when the muscle dies it does not go into relaxation, but passes directly from life into post-mortem rigidity.

Respiration.—Both Langgaard and Fraser affirm that the fatal result in poisoning by strophanthus is due to cardiac arrest, but Mairet and Combemale,[6] and also Bahadhurji state that at least in some instances there is a primary arrest of respiration, and, according to Mairet and Combemale, the respiration which is at first hurried is usually distinctly slowed before the fatal termination. There is, however, no sufficient proof that the drug acts upon the respiratory centres, and though asphyxial death does occur, it is in all probability the result of the muscular influence of the poison.

Circulation.—Dr. Fraser proved that strophanthin has a direct action upon the heart of the frog, and in this has been confirmed by Bahadhurji, by Huchard,[7] by Reusing, by Gley and Lapicque,[8] and other observers. By minute doses the rate of the beat is lessened and the size and force of the aortic pulse-wave increased.

The action of strophanthus upon the heart is certainly very similar to that of digitalis, but the assumption by some investigators that the two influences are identical does not seem to us justified. Reusing found strophanthin to be about twenty times as strong in its influence upon the isolated heart as is digitalin, and also more permanent in its effects, as the heart arrested by digitalis could be restored by washing out with fresh serum, a process which had no influence when the cardiac arrest was due to strophanthin. It is noteworthy that Fraser and some other investigators have found that the frog's heart is arrested in systole, whilst Reusing and Huchard have seen it stop in diastole, and Paul Bert has noted in the cat both systolic and diastolic arrest. The muscle of the frog's heart, according to Fraser, is much more susceptible to the influence of strophanthin than the voluntary muscles, and passes rapidly into post-mortem rigidity, with acid reaction.

The combined testimony of Fraser, of Popper,[9] of Gley, of Paschkis and Zerner,[10] of Langgaard, and other investigators proves that moderate doses of strophanthus cause in mammals pronounced rise in the arterial pressure. As this occurs as well in curarized (Gley) as in normal animals, it must be due to a direct action of the drug, and not secondary to changes in the respiration ; after poisonous doses the pressure immediately or secondarily falls gradually to zero. The sphygmographic work of Paschkis and Zerner shows that strophanthus influences the blood-pressure in man as it does in the lower animals. The rise of blood-pressure is certainly, at least in part, due to stimulation of the heart, but in regard to

the influence of the drug upon the blood-vessels we have not satisfactory experimental information. Bahadhurji asserts that they seem to be contracted under the influence of the drug. Popper found that section of the splanchnic nerve or of the cervical spinal cord does not prevent the rise of the arterial pressure, so that if the vessels are affected it is probably by a direct action upon their muscular coats.* The known wide-spread muscle-action of the drug indicates that it has this stimulating influence, and that narrowing of the blood-paths by direct stimulation of the muscle-fibres in the walls of the arterioles is a factor in the phenomena of strophanthus action. The cause of the fall of pressure has not been determined.

The slowing of the pulse is probably due to the direct action of the drug upon the heart, Paschkis and Zerner † having found that in the dog it is not prevented by previous section of the vagus ; Popper states that in the advanced poisoning there is peripheral paralysis of the vagus without alteration of the irritability of the accelerator nerves.

Diuretic Action.—Although several observers have failed to notice an increase in the urinary secretion in man and in animals under the influence of strophanthus, yet the general testimony is too strong to be gainsaid ; and it seems established that strophanthus acts, not only in cases of cardiac disease, but also in healthy men and animals, as a powerful diuretic. This indicates that the drug has a direct stimulating influence upon the secreting structure of the kidneys, a conclusion which is confirmed by the renal lesions of the poisoning, and also by the oncometric experiments of Phillips, who found the size of the kidneys not affected by the drug,—*i.e.*, that it produced no pronounced congestion of the kidneys.

SUMMARY.—Strophanthus is primarily a muscle-poison, whose influence, whatever it may be upon the nervous system, is so subordinate to its action upon the voluntary muscles and upon the circulation as to play little or no *rôle* in the poisoning. In concentrated form, however, it is paralyzant to the sensory nerves and probably to other portions of the nervous system. The most susceptible portion of the body to its influence is the cardiac muscle, upon which and also probably upon the muscular fibres of the walls of the vessels it acts as it does upon voluntary muscles.

THERAPEUTICS.—Strophanthus is used in practical medicine to meet exactly the same indications as those for which digitalis is prescribed. It is, however, less powerful and less certain in its influence for good than is digitalis, but acts more promptly and more fugaciously. Its influence usually begins in half an hour and lasts from four to eight hours. It would seem to be indicated especially in cases of acute heart-failure, but both its tincture and strophanthidin are locally too irritant for hypodermic

* In Popper's experiments the pressure in the pulmonary artery rose much less than that in the aorta, and the pressure in the veins was very little altered.

† These observers state that sometimes in the normal dog the slow pulse was wanting.

use except in cases of great emergency. When actively pushed, it probably is no better borne by the stomach than is digitalis ; but experience has shown that some individuals are affected unpleasantly more quickly by strophanthus than they are by digitalis, whilst in others the opposite is the case. In *chronic heart disease* strophanthus stands next to digitalis in the list of useful heart tonics and stimulants, in some cases acting more favorably than digitalis for reasons not apparent, in others extremely useful in combination with digitalis, whilst in the majority of instances it is chiefly advantageous as a remedy to take the place of digitalis when it is from time to time suspended for the purposes of resting the stomach or of preventing cumulative action. Its superiority as a diuretic makes it of especial value in cases of *pulmonic œdema* or of *general cardiac dropsy*. When given in overdose it produces burning in the œsophagus and the stomach, with gastric distress and severe vomiting.

M. Furbringer[11] reports three cases in which, after the remedy had been used in a large quantity and for a long time, sudden death from syncope occurred. It may well be that the death was directly caused by the strophanthus, but it is more probably a parallel occurrence to what often happens in advanced cardiac disease treated with very large doses of digitalis (see page 311).

Zerner and Loaw[12] have employed strophanthus with alleged success in *Basedow's disease* and in *Bright's disease*, and they consider it especially useful in renal affections with secondary failure of the heart, a condition in which we have seen it act most advantageously. Rothziegel and Koralzewski[13] and H. Haas[14] commend it highly, not only in chronic but also in acute Bright's disease.

The pharmacy of strophanthus is at present very unsatisfactory. The five per cent. tincture (TINCTURA STROPHANTHI, U. S.) has been almost exclusively employed in doses of from five to ten minims (0.3–0.6 C.c.) every six to eight hours. As the crude drug contains from one-half to one per cent. of strophanthin, five minims of the tincture represent from one- to two-thousandths of a grain. The strophanthin has, however, been used by Rothziegel and Koralzewski, and by others, in much larger doses. These authorities state that the proper dose is from one-three-hundredth to one-two-hundredth of a grain (0.0002–0.0003 Gm.). Stahr[15] affirms, as the result of clinical studies with Merck's crystalline strophanthin, that twenty milligrammes, or three-tenths of a grain, may be given in twenty-four hours without producing serious results. On account of the certainty of its influence, strophanthin will be preferable to the cruder preparations when a pure commercial article of known dose is afforded.

CAFFEINA—CAFFEINE. U.S.

Caffeine occurs in long, snow-white, silky, opaque, odorless crystals, sometimes conjoined into feathery crystals, of a feeble bitter taste. It has a neutral reaction, but unites with acids to form salts. It is soluble, at 59° F., in eighty parts of water, thirty-three parts of alcohol, five hun-

dred and fifty-five parts of ether, or seven parts of chloroform. It was first discovered in coffee by Runge,[1] in 1820. In 1827 Oudry discovered a principle in tea which he called *theine*, which in 1838 was proved by Mulder and C. Jobst to be identical with caffeine. Martius, Stenhouse, J. Attfield, and other chemists have also shown that caffeine is the active principle of *Guarana* (the fruit and leaves of the Paullinia sorbilis of Brazil), of *Mate*, or *Paraguay tea* (the leaves of the Ilex Paraguaiensis),* and of the *Kola nut* of Africa (Cola acuminata). H. M. Smith[2] has also found it in *Yaupon* (the leaves of our native Ilex Cassine). Commercial caffeine is obtained in great part from tea which has been more or less damaged during transmission or has been originally unfit for use as a beverage.

CAFFEINA CITRATA, U. S. (*Citrated Caffeine*), often incorrectly termed *citrate of caffeine*, is a mixture of caffeine and citric acid. It is a white bitter powder, soluble in about three parts of water, and contains about fifty per cent. of caffeine.

Local Action.—Absorption and Elimination.—Caffeine is not irritant, and for practical purposes may be considered to have no local action, except it be upon the sensory nerves. It is absorbed rapidly and eliminated chiefly through the kidneys; when in large amount in part unchanged, when in small quantity entirely altered (Richard Schneider,[3] also E. Rost[4]). According to M. Albanese,[5] at least a part of the caffeine (trimethylxanthine) appears in the urine as dimethylxanthine, monomethylxanthine, or even xanthine.

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* *Mate* is used in South America very largely as a substitute for tea. According to the analyses of Peckolt, of Rio Janeiro, it contains 2.5 parts in a thousand of caffeine; but M. Byanon found 1.85 per cent. of the alkaloid (*Bull. Thérap.*, xciii.). It is sold in two forms: *mate in leaf* is prepared as ordinary tea is, and taken with sugar and milk to taste; *mate in powder* is prepared by pouring upon the powdered mate boiling water, and the infusion is sucked up through a tube, the bulbous end of which is furnished with a fine sieve, or the powder is thrown into boiling water, and when the mixture recommences boiling, cold water is poured into it; this precipitates the powder, and the infusion is taken clear.

M. L. Lapicque (*Compt.-Rend. Soc. Biolog.*, 1890, ii.), in comparative experiments made upon himself, found that kola nut and caffeine had exactly similar effects. Edouard Heckel (*Rept. de Pharm.*, October, 1892) asserts that whilst the kola nut has a muscular action similar to that of caffeine, its stimulating effect is more powerful and more prolonged. For an elaborate study, see *Die Kola Nuss*, Bernard Schuchardt, 1889.

Chemically the alkaloid obtained from tea and known as *theine* is identical with caffeine. Thomas J. Mays asserts, however, that theine principally influences sensation, while caffeine does not; that theine produces spontaneous spasms and convulsions, while caffeine does not; that theine impairs the nasal reflex early in the poisoning process, while caffeine does not, if at all, until in the very last stage; that the lethal dose of theine is larger than that of caffeine. Mays also affirms that theine is a powerful local anæsthetic, while caffeine is not. A comparison of the various papers of Mays (*Trans. Coll. of Physicians*, Phila. 1866, viii. 365; *Journ. of Physiology*, vii. 458; *Therap. Gaz.*, 1885, 1886; *The Polyclinic*, v.) has not seemed to us to confirm these alleged differences, which also are at variance with the results obtained by Brunton and Cash (*Journ. of Physiology*, ix.), and the clinical results obtained by Mays have not been corroborated.

Guaranine is also thought by Mays to be distinct in its physiological action from caffeine. Indeed, it seems to stand half-way between theine and caffeine in its influence. It is not certain that the alkaloids used by Mays were pure.

General Action.—The peculiar wakefulness, the increased mental activity, and the nervous restlessness which are induced by strong coffee are familiar phenomena to almost every one. They are without doubt largely, if not altogether, due to the caffeine contained in the beverage.* By doses of four or five grains of the alkaloid a somewhat similar state of body and mind may be induced. Lehmann found that eight grains of caffeine produced increased frequency of the pulse, very frequent urination, tremulousness, excited mental action, passing into a form of delirium, with confusion of thought, visions, and finally a deep sleep. About two hours after taking twelve grains, Pratt was seized with intense physical restlessness, conjoined with a very uneasy condition of the mind ; very marked general muscular tremulousness soon followed, and the mental anxiety increased. After this state passed off, there was obstinate sleeplessness, with active and persistent thinking, and frequent urination.

According to various observers, the chief symptoms induced by poisonous doses of caffeine in the frog are muscular quietness and weakness, with disturbance of respiration, succeeded by a stage of violent tetanic convulsions, ending in general paralysis and death by asphyxia, the heart beating after the cessation of respiration, although evidently much affected.†

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* The infusion of roasted coffee differs in its action on human individuals so much from tea, and according to general belief from the infusion of green coffee, that as long ago as 1853 J. Lehmann experimented with the empyreumatic oil of coffee, and reached the conclusion that it was an active substance. The results obtained by the various experimenters upon what has been called by some *caffeone* have been strangely contradictory, and it does not seem necessary here to follow out this matter in detail, but only to call attention to the recent researches of Hare and Marshall (*Med. News*, Phila., lii.), and of E. T. Reichert (*Ibid.*, 1890, lvi.), whose papers contain a discussion of the whole evidence. Hare and Marshall believe that they have proved that the empyreumatic oil is active; Reichert, however, believes that the changes produced by it in these experiments were due to mechanical alterations in the circulation by the insoluble oil, affirms that he has obtained the same results by the intravenous use of pure olive oil, and asserts that the oil of coffee given subcutaneously has no general effect upon the organism. It seems to us, however, that further researches are necessary before the statement of Reichert, that the empyreumatic oil of coffee is inactive, can be considered as established, and that in any case there must be formed some active principle, volatile or otherwise, during the process of roasting coffee; probably the caffeine itself is in part changed into some new compound.

† See Albers (*Deutsche Klinik*, 1853, 370), Falck and Stuhlmann (*Virchow's Archiv*, xii. 365), Mitscherlich (*Der Cacao und die Chocolade*, Berlin, 1859), I. Hoppe (*L'Écho Méd.*, 1858), Brill (*Inaug. Diss.*, Marburg, 1861), Oscar Johannsen (*Inaug. Diss.*, Dorpat, 1869), and others. The minimum fatal dose is stated by Leven (*Arch. de Physiol.*, 1858) to be .015 grain in a frog of moderate size.

Johannsen denies the existence of true convulsions in the frog, asserting that there is only a rigidity due to an effect upon the muscles.

Buchheim and Eisenmenger (quoted by Schmiedeberg) corroborate the muscular changes noted by Johannsen, but insist that there are also true nervous convulsions. O. Schmiedeberg (*Archiv für Exper. Pathol. und Pharm.*, ii.) believes that he has reconciled these differences of observation by finding that the alkaloid acts much more powerfully upon the muscles of Rana temporaria than upon those of Rana esculenta; so that a dose of caffeine which causes intense general muscular stiffness in the former produces in the latter only true convulsions, the convulsions in R. temporaria being prevented or masked by the disorder of the muscles. The most recent researches (E. Leblond, *La Caffèine*, Paris, 1883; W. Filehne, *Arch. f. Anat. und Physiol.*, 1886) indicate, however, that the differences depend to some extent upon the size of the dose, but in still greater

In birds poisoned with caffeine the symptoms (Brill[6]) are irregular movements, apparently to some extent due to cerebral disturbance, increased rapidity and irregularity of respiration, spasmodic tremblings, and tetanic and clonic convulsions, with paralytic phenomena. In mammals the results of the toxæmia, as noted by various observers, are restlessness, hurried respiration, at first a slight lowering and afterwards a decided elevation of temperature, muscular weakness, tetanic and clonic convulsions, increasing general paresis, and finally death, apparently from paralytic arrest of respiration.*

Cerebrum.—There is no evidence that caffeine exerts a very marked influence upon the cerebrum of the frog, or even of some of the lower mammals, unless the convulsions induced by it are believed to be partly the result of some such action. In certain of the higher animals, such as the cat, it often produces a condition of almost frantic cerebral excitement. In man the increase of brain-power produced by coffee, tea, guarana, and other drugs containing caffeine and the allied alkaloids is undoubtedly real, and we must conclude that caffeine is a powerful *stimulant to the cerebral cortex*. It appears to us to be our most certain and effective stimulant of the nerve-centres connected with the intellectual functions. Those centres whose function is consciousness are greatly stimulated, and wakefulness results ; while again, in contrast with opium, caffeine increases the activity and power of the reasoning faculties at least as much as it does that of the imagination. Coffee prepares for the active work, both mental and physical, while opium leads its votaries to the dream-land of poets.

Spinal Cord.—There has been much discussion as to the method in which caffeine produces convulsions in the frog, but it seems to be established that they are, at least in part, of spinal origin. They are not prevented by section of the cord high up (Pratt and Leblond), therefore they are not cerebral : they are prevented by destruction of the spinal cord (Leven[7]), and would appear, therefore, to be spinal.

The difficulty of interpretation of the phenomena has arisen from the fact that the muscular action of the alkaloid in a measure masks its influence upon the spinal cord, there being both muscular stiffness of purely muscular origin and convulsions of spinal origin. This was clearly demonstrated by Pratt, who found that though destruction of the lower portion of the spinal cord prevented the convulsions in the hind legs of the frog, it did not interfere with the development of the contractures. Further, Pratt included all the tissues of a frog, except the spine, in a tight ligature just above the bifurcation of the aorta, and administered caffeine, when the anterior legs became very stiff, and had also occasional severe convulsions, in which the hind legs participated, although between the paroxysms they were perfectly relaxed.

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degree upon variations in the sensitiveness of individual frogs; thus, Kobert (*Arch. f. Exper. Path. u. Pharm.*, xv.) found that frogs of the same species are very much more susceptible in the spring than in the autumn. The rigidity and paralysis are muscular.

* In an elaborate series of experiments, Bennett (*British Medical Journal*, 1874) found that the fatal minimum dose of the poison for the cat and the rabbit was a little over a grain for the pound, five and a half grains being required for a five-pound animal.

The conclusion seems established that in the frog caffeine *acts as a motor spinal stimulant and also as a muscle-poison.** The physical restlessness and tremulousness produced in man by excessive doses of coffee and tea, and the convulsions of caffeine-poisoning, are probably both spinal and cerebral, though our knowledge of this matter is incomplete.†

Nerves.—The motor nerves appear not to be affected, but the sensory nerves are apparently slightly affected.

Alexander Bennett[8] has found that after death from theine the motor nerves retain their normal susceptibility, and Pratt surrounded one crural nerve of a frog with a paste "of theine and water," and irritated the spinal cord, when both legs responded with uniform alacrity. Bennett also tied the crural artery of a frog, poisoned it with the alkaloid, and found that irritation of the cord produced equally active contractions in the two legs. The chief evidence as to the sensory nerves is furnished by Pratt, who found that when the left sciatic nerve of a frog was surrounded by a paste of theine and water, after ten minutes irritation of the right foot produced reflex movements, while irritation of the left foot failed to elicit any response. Leblond[9] has noted marked hyperæsthesia in the frog, and Rumpf[10] affirms that increased sensibility of the skin can be demonstrated in man.

Muscle.—The action of caffeine upon the muscle is readily demonstrated by throwing the isolated gastrocnemius of the frog into a one per cent. or even a weaker solution ; in from two to three minutes the muscle becomes markedly contracted, swollen, round, stiff, and unable to respond to the galvanic current. That it is the muscle-fibre which is affected is shown by the experiments of Pratt, who found that when an isolated muscle was soaked in a solution of curare until the nerves were killed, and then thrown into a solution of caffeine, the usual rigidity was developed. The elaborate studies of Leblond appear to prove that there are two stages (as in veratrine-poisoning) in the action of caffeine upon the frog muscle,—a primary stage, with exaggerated muscular excitability and a tendency to prolonged tetanic contractions after momentary stimulation, and a final stage of rigidity and lost excitability.‡ W. Sobieranski[11] believes that his ergographic experiments prove that in fatigue caffeine not only stimulates the nervous system and thereby increases working power, but also acts directly upon the muscle.

According to the researches of Paschkis and Pal,[12] it would appear to be the xanthine which influences the muscle-fibre, since these investigators found that caffeine (trimethylxanthine), theobromine (dimethylxanthine),

* Alexander Bennett has brought forward the theory (*loc. cit.* and *British Medical Journal*, 1874) that caffeine paralyzes the posterior columns of the cord without affecting the anterior columns; but his evidence appears to us insufficient to prove his conclusions. He grounds his belief chiefly on finding that in poisoned frogs and rabbits galvanization of the posterior columns of the exposed cord produced either no muscular contractions or only such as were very much more feeble than those provoked by galvanization of the anterior columns.

† Uspensky (*Reichert's Archiv*, 1868, 526) has found that forced artificial respiration in great measure suspends the convulsions.

‡ Johannsen states that when a muscle under the microscope is touched with caffeine, its fibres can be seen to contract half their length.

and xanthine shared the activity ; caffeine being the strongest, xanthine the weakest.

Circulation.—Caffeine has a direct influence upon the heart, although that viscus continues to beat in animals poisoned by the drug after the cessation of respiration.

According to Voit (quoted by Brill), in the frog the rapidity of the cardiac pulsation is at first increased, but the pulsations become slower and slower, and are accompanied by irregularity of rhythm, the heart finally ceasing to act, but still responding to stimuli at a time when the voluntary muscles are absolutely dead. Falk and Stuhlmann,[13] and Johannsen [14] observed that caffeine first increases and then lessens the frequency of the cardiac pulsations in the frog. According to Johannsen, the lessening of the frequency comes on the more quickly and the more powerfully as the size of the dose is increased. After a time the heart begins to beat irregularly, with short intermissions, which, as time goes on, grow longer and longer, till at last movement ceases. Johannsen found that the action upon the cut-out frog's heart was the same upon the viscus *in situ ;* Leblond confirms this, and states that the heart is finally arrested in systole ; so also does Thomas J. Mays.[15] Aubert and Haase [16] find that the action of the alkaloid upon the pulsations of the frog's heart varies greatly ; and indeed the individual experiments of the authors previously quoted show such variation. This is confirmed by the research of Rioschiro Maki.[17] This investigator experimented upon the cut-out frog's heart with the Williams apparatus, and found that the pulse was variously affected. In most of his experiments the arterial pressure—*i.e.*, the heart's work—was markedly lessened, but in a few cases it was distinctly increased.

The conclusion that caffeine exerts a double influence upon the frog's heart, *in small doses stimulating it and increasing its work, and in larger doses paralyzing it*, seems to be confirmed by Paul Faval,[18] who finds that in a proportion of ten centigrammes to one hundred and fifty grammes of artificial blood the alkaloid reinforces the isolated frog's heart, giving its contractions more amplitude and more energy, but that stronger doses depress the heart, and finally arrest it in diastole ; and by H. C. Beyer,[19] who has reached similar conclusions with the terrapin's heart.

The results obtained by various experimenters as to the influence of caffeine on the circulation in mammals are in their general appearance contradictory, but are, however, we believe, reconcilable.

In attempting such reconciliation it seems better to discuss separately the effects of the drug upon arterial pressure and pulse-rate. In the Aubert and Haase experiments, caffeine usually produced pronounced fall of the arterial pressure, although in one experiment there was a distinct rise. It is to be noted that the research was made with enormous doses of caffeine, and usually upon dogs under the influence of narcotics. In two experiments upon alcoholized dogs, Binz [20] obtained a pronounced rise of the arterial pressure ; while Maki, experimenting upon animals under the influence of atropine or chloral, obtained after large doses a distinct fall of the arterial pressure, which in a few cases was preceded by a rise. It is evident that the method of research employed in these experiments makes it impossible to draw any very positive conclusions. In normal animals, Leven found in the first stages of caffeine-poisoning a distinct increase of the arterial pressure, and in the elaborate experiments of Reichert [21] it was noted that in the normal dog

caffeine injected into the jugular vein, in moderate amount, caused a primary fall of pressure (evidently due to an overwhelming effect of the concentrated alkaloid upon the heart), followed by a rise above the normal, followed in turn, if the dose had been large enough, by a marked fall of pressure. Very large doses of caffeine produced a persistent fall of pressure, ending in final diastolic arrest of the heart. In none of Reichert's experiments was the rise of arterial pressure very great, but, except after heavily toxic doses, it occurred almost invariably. Leven asserts that after he had divided the pneumogastrics and sympathetics and isolated the heart from all the nerve-centres, caffeine still increased the arterial pressure; while Reichert states that not only is the increase of the pressure seen when the animal is motionless with curare, but also after destruction of the vaso-motor centres in the medulla oblongata.

The total evidence seems to us conclusively to show that *caffeine increases the arterial pressure independently of the vaso-motor centres.* Reichert believes the rise to be due to an action on the muscle-fibre in the walls of the blood-vessels. But we have no direct proof of the correctness of this, while all the experiments upon the frog's heart (see preceding paragraphs) indicate that in *small doses* the drug acts *upon the heart* as a *direct stimulant.* It is, however, altogether probable that the muscle-fibre in the arterial walls shares in the general action of the alkaloid upon muscles.

In the advanced stages of caffeine-poisoning *both the heart and the vaso-motor system are without doubt depressed*, so that the cause of the fall of pressure is duplex.

In regard to the *pulse*, Aubert notes as a constant effect an increase of the pulse-rate, and this appears to be the most frequent result produced by caffeine; but it has been shown by Reichert that under certain circumstances there is a slowing of the pulse.

Leven asserts that the increase of the pulse-rate is to be seen after isolation of the heart from the nervous centres, and is, therefore, due to an action upon the heart itself, a conclusion which is in accord with the general results of observations upon the isolated frog's heart, and is confirmed by Reichert, who believes that there are paralyses of the cardio-inhibitory centres, both in the medulla oblongata and the heart. The slowing of the pulse occasionally seen in the first stages of the poison Reichert attributes, with probable correctness, to a primary stimulation of these cardio-inhibitory centres; the alteration of the pulse which sometimes occurs in advanced poisoning he believes to be due to a direct action of the drug upon the heart. Some authorities are of the opinion that the drug stimulates the cardiac accelerators.

Diuretic Action.—In poisoning by caffeine great increase in the secretion of urine is a common symptom, and the statement of Gubler,[22] that the alkaloid is one of our most powerful and certain diuretics, has received abundant confirmation. The effect of the drug upon healthy men would indicate that in dropsies it does not act simply by regulating the circulation of the kidney, but has also a distinct effect upon the renal organ itself.

That caffeine acts directly upon the kidneys was proved by W. von Schröder and by A. Langgaard,[23] who separately found that when a canula was inserted into

the ureters in an animal whose vaso-motor system was completely paralyzed by chloral, injections of caffeine into the circulation caused a very great increase in the urinary secretion. Langgaard found that usually before the great increase of diuresis the urinary secretion was arrested for several minutes. This is in exact accord with the experiments of C. D. T. Phillips[24] made with Roy's oncometer. It was found that immediately after the injection of a small dose of caffeine, when the blood-pressure was either slightly depressed, elevated, or unaffected, the kidney underwent a very distinct contraction of its volume, which lasted for two or even three minutes and was accompanied by great lessening or arrest of the urinary secretion. After the contraction, the kidney rapidly expanded beyond its original bulk, and at the same time the urinary secretion became excessive. Phillips's facts do not, as he seems to think, prove that the diuresis is caused by the increase in the flow of the blood to the kidneys. It is more probable that the condition of the local blood-vessels is the result of the action of the drug upon the renal secreting organ; especially is this the case since Schröder found that the division of all the renal nerves did not prevent the increase of the secretion under the action of caffeine. Because the secretion from the uninjured kidney was increased much more than from the kidney whose nerves were destroyed, Schröder believes that the drug increases diuresis by acting both upon the nerve-centres and upon the secreting structure of the kidney. To our thinking, however, the direct injury to the secreting apparatus of the kidney by division of the renal nerves is sufficient to account for the difference between the influence of the alkaloid upon the normal and the operated-upon kidney, without necessitating the theory of a twofold action. Schröder found that there was an increase not only of the liquid, but also of the solids of the urine.

Temperature.—We know of no recorded temperature-curves of caffeine-poisoning in man. It is probable, however, that the effect of the alkaloid is precisely what it is in other mammals. Binz states that in animals minute doses have no effect upon the bodily temperature; doses just enough to produce slight toxic symptoms cause a rise of 0.6° C.; excessive doses cause an elevation of 1° to 1.5° C., the maximum being reached in one to two hours; doses which rapidly kill have very little effect upon the temperature.

General Nutrition.—The enormous use made by mankind of substances containing caffeine indicates that in some way it is directly of service in the wear and tear of daily life. It is not probable that any of the caffeine is assimilated, but it is thought by some authorities to check very greatly the elimination of nitrogen, or, in other words, to lessen the waste of tissue.

This subject was laboriously investigated by Julius Lehmann in 1853, and by F. W. Böcker[25] in 1854, and earlier. Lehmann found that the exhibition of six grains of caffeine daily, the regulated diet being uniform, diminished the elimination of urea from twelve to twenty per cent. Upon experimenting with the empyreumatic oil of coffee he found that it lessened even to a proportionately greater extent the elimination of urea, and also acted very powerfully in producing sleeplessness, so that the favorite beverage is by no means dependent upon its contained caffeine for all of its activity. Böcker[25] published his first researches on coffee in 1849, but we have never seen any abstract of the article, other than the statement that he found that the drug causes diminished elimination of urea. His investigation of the effect of tea[26] was most elaborate and laborious. He analyzed the fæces, the urine, and

the products of respiration, and found, a similar diet being maintained, that tea did not affect sensibly the elimination of carbonic acid from the lungs, but did very decidedly diminish the excretion of urea, and also of nitrogenous matters in the fæces. He then tried abstaining from food for periods of thirty-six hours, with and without the use of tea, with results perfectly in accord with those just stated. The results obtained by other experimenters are, however, singularly discordant. Henri Hoppe[27] found that in the dog coffee diminishes very slightly the urea-elimination, but greatly increases the output of carbonic acid. In regard to urea, Rabuteau and his pupil Eurastratiade, working with coffee upon men and dogs, obtained results similar to those of Böcker,[28] as did also Hammond in this country. On the other hand, C. G. Lehmann,[29] Voit,[30] and Roux [31] found that caffeine or coffee sensibly increases the elimination of urea, or, in those accustomed to the daily use of coffee, has no influence. In a long series of experiments upon dogs by Couty, Guimaraes, and Niobey,[32] it is affirmed as a uniform result that the use and assimilation of nitrogenous food were greatly increased, that the carbonic acid and oxygen in the blood were markedly decreased, and that the proportion of sugar and of urea in the blood was notably increased.

In the face of so much contradiction it is perhaps wisest to reserve opinion, but it does seem as though the present evidences warranted the conclusion reached by E. Perisot[33] that the action of caffeine upon urea-elimination and upon protoplasmic change is inconstant, and not direct and pronounced. It is true that in a long series of very elaborate calorimetrical experiments performed by E. T. Reichert[34] it seems to have been proved that caffeine increases the heat-production as well as the heat-dissipation, and that of these phenomena, the increase of the heat-production is probably primary. This result is in accord with that of Wilhelm Heerlein,[35] who found marked increase in the consumption of oxygen and formation of carbonic acid produced under the influence of caffeine. Nevertheless, these united results, if their accuracy be accepted, do not show that destructive metamorphosis of nitrogenous tissue is increased by caffeine, but only that there is an increased destruction of carbohydrates.

SUMMARY.—Caffeine is a powerful stimulant to those cells of the cerebral cortex which are functionally connected with consciousness and intellectual action. It is also mildly stimulating to the respiratory centres and probably to the motor cells of the spinal cord, but seems to be without action upon the nerve-trunks. It is a powerful muscle-poison, at first producing a condition in which there is exaggerated muscular excitability, with a tendency to tetanic contractions upon momentary stimulation, and afterwards a stage of stiffness, weakness, and, finally, lost excitability. It is a mild stimulant to the circulation; probably by virtue of its relation to the muscle-fibres it increases the cardiac force and perhaps also directly contracts the arterioles. In overdose it depresses the circulation, probably acting both upon the heart and the blood-vessels. It is absorbed with rapidity, and is to some extent decomposed in the body, and, at least in part, eliminated through the kidneys, upon whose secreting structure it exerts a marked stimulating influence. Although the evidence is contradictory, it is not at present writing probable that caffeine has any distinct specific influence upon protoplasmic nutrition, but it does appear to directly increase the production of carbonic acid and of animal heat.

THERAPEUTICS.—In accordance with its physiological action, caffeine is employed in practical medicine as a cerebral and cardiac stimulant. It is often taken to produce wakefulness and increase the mental power during excessive work. It is a valuable remedy for the relief of *migraine* and other forms of *nervous headaches*, in which its effects are sometimes marvellous, although more often it fails to accomplish good. To predict in any case what its influence will be, in the present state of our clinical knowledge, is impossible ; but the remedy may always be tried in safety in the dose of five grains, taken when the paroxysm is coming on, and repeated in half the quantity once in forty minutes if necessary. It is in these cases especially effective in combination with phenacetin (proportion five grains to fifteen grains). In *opium-poisoning*, either in the form of unlimited quantities of a strong decoction of coffee or of the alkaloid itself, it is a standard remedy, acting by promoting wakefulness and stimulating the respiration.

J. Hughes Bennett found that the exhibition of from four to four and a half grains of caffeine would save a proportion of cats poisoned with the previously ascertained minimum lethal dose (one and seven-eighths grains) of morphine. Several of the cats which had thus been saved succumbed some days afterwards to one and seven-eighths grains of morphine. The caffeine was powerless to save animals to which larger doses of the narcotic had been given.

We have had no experience with the use of caffeine as a general stimulant in *acute adynamia*, but various French authors recommend the remedy very highly, and H. Huchard[36] especially commends it in *typhoid fever*, asserting that it relieves not only the adynamia, but also acts as an antipyretic, and through its diuretic influence is especially useful when the urine is scanty and albuminous.

Caffeine is valuable as a cardiac stimulant in the treatment of all forms of heart-failure. The statement of Gubler that it acts as a powerful diuretic is also undoubtedly correct. The indications for its employment are precisely those which call for the use of digitalis, but it meets these indications with much less certainty than does that drug. Caffeine, unlike the digitalis group, finally paralyzes the heart, and therefore does not compare as a cardiac stimulant in power and completeness of action with digitalis or strophanthus, belonging rather with ammonia and alcohol. It is, however, more prompt and fugacious in its action than is digitalis, and much more actively diuretic ; and is, therefore, especially useful when there are pronounced dropsical symptoms. In *chronic Bright's disease* it is often of service, especially in the latter stages, when there is marked cardiac failure. In *acute Bright's disease* it should be employed with caution, if at all. It is superior to digitalis in never disagreeing with the stomach and in having no distinct cumulative tendency. In some cases, however, it produces obstinate wakefulness, and we have occasionally found it necessary to give it solely in the early part of the day. It is usually best to commence with a dose of four grains, given

twice daily, increased if necessary to twenty or twenty-five grains a day. For internal administration the citrated caffeine is often preferred on account of its solubility. When great promptness of action is required, as in cases of sudden *collapse* or of sudden *cardiac failure*, the hypodermic use of caffeine suggests itself. Unfortunately, the ordinary salts are decomposed in the presence of water, and are, therefore, ineligible for hypodermic use. The *sodium and caffeine benzoate* has been proposed as moderately stable and free from irritating properties. One equivalent of sodium salicylate (160 parts) will also cause the solution of one equivalent of caffeine (244 parts), and the following formula has been commended by Tanret for hypodermic use: sodium salicylate, thirty-one parts; caffeine, forty parts; distilled water, sixty parts.

Toxicology.—The only case of poisoning by caffeine that we have met with is reported by C. H. F. Routh.[37] An adult took a drachm of the so-called citrate. The symptoms developed at once; they were burning in the throat, giddiness, faintness, nausea, numbness and tremors of the extremities, pain in the stomach and bowels, profuse diuresis, and finally collapse, with cardiac oppression and icy extremities. Consciousness was not impaired, and there was no headache until the patient began to recover. In a case reported by Curschmann,[38] a woman, in order to produce an abortion, took a decoction made from about eight ounces of freshly roasted coffee. Two hours later she was found in a condition of great anxiety, with a sensation of intense need for air; she was exceedingly restless, and continually attempted to get up from her chair, but was powerless to do so. All the extremities, but especially the hands, were affected with very pronounced choreic tremors. She knew persons and her surroundings, but her cerebration was very much affected, and the next day she remembered nothing that had happened at this time. The respiration was quick, 24 and 25 per minute, and short; the pulse 112; the heart-beats very strong, even violent. One hour after the ingestion of the dose violent diarrhœa set in, and continued until the next day. The passages were very thin and watery, with but little violent pain, but much tenesmus. There was also marked tenesmus of the bladder. The urine was greatly increased in quantity, with a specific gravity of 1014.

CONVALLARIA. U.S.

In 1859 G. F. Walz discovered in the *lily of the valley* (*Convallaria majalis*, the rhizome and roots of which are official) two active substances, *Convallarin* and *Convallamarin*. Of these, the first is crystalline, insoluble in water, and, according to W. Marmé,[1] when taken in doses of three or four grains, acts as a simple purgative. The glucoside convallamarin is soluble in water, and is the principle to which the plant owes its action upon the circulation. Marmé found that it kills by a direct action upon the heart, and in moderate doses first slows and then quickens the pulse: previous division of the vagi did not interfere with the development of these phenomena. Sée[2] finds that in the dog it first

slows the action of the heart and increases the blood-pressure decidedly, the respirations at the same time becoming fuller and a little less frequent. If a toxic dose has been given, the heart's beats become very rapid and irregular, the arterial pressure still being much above normal; finally the pressure begins to fall, the cardiac pulsations to grow more feeble, and death occurs through syncope. It is stated that the pneumogastric nerves are weakened but never paralyzed, while the general nervous system is not affected. In man the action of the drug upon the circulation is as in the lower animals, and there is said to be usually produced profuse diuresis and sometimes purging. In Isaew's experiments upon frogs with convallamarin, the heart was arrested in ventricular systole by two milligrammes of the pure convallamarin, the frog continuing to live for a long time, the remedy seemingly having no effect upon its general nervous or muscular system; isolating the heart had no effect upon the action of the poison.

The fact that the heart is arrested in systole by convallamarin has been confirmed in the frog by Coze and Simon,[3] in the dog by I. Ott,[4] and it would appear, therefore, that the drug is a cardiac stimulant, more or less similar to digitalis in its action. Unfortunately, however, Sée affirms that in the dog the heart is arrested in diastole, that organ not being able to respond to the most powerful galvanic stimulant; Leubuscher states that convallamarin causes in the frog systolic cardiac arrest, but diastolic cardiac arrest in the mammal; and further, that in no doses does it in the mammal elevate the arterial pressure; whilst Leo Löwenthal,[5] using the same preparation in exactly the same manner and dose upon different frogs of the same species, obtained diverse results which he himself was at a loss to explain. The evidence is so contradictory as to suggest that different observers have used different substances under one name. J. Nathanson[6] asserts that the confusion is largely due to the impurity and lack of genuineness in the products used, even Merck himself having admitted that his commercial convallamarin is not the pure principle. Nathanson found that convallarin produced in man when given in doses of 0.06 to 0.12 gramme three or four times daily only nausea, diarrhœa, and gastric pain; while convallamarin administered in daily amounts gradually increasing from 0.03 to 0.3 gramme reduced the rate of the pulse and markedly increased the flow of urine, only in very rare cases causing nausea or vomiting.

THERAPEUTICS.—The lily of the valley is said to have been long used by the Russian peasantry for the relief of dropsy, and in 1880 Troitzky and Bojojawlewsky[7] called attention to it as a valuable remedy in *cardiac valvular disease*, especially when associated with *dropsy*. Sée recommends it in *palpitation of the heart*, *cardiac dilatation*, *fatty degeneration*, and other forms of cardiac weakness, also in *valvular lesions* with failing heart-power; in a word, in the class of cases in which digitalis is now used. When there is dropsy, its positive diuretic action renders it especially valuable, and in some cases it purges freely, probably through

the convallarin. The value of the remedy has been confirmed by H. Desplats[8] and by several other practitioners. Although condemned after trial by B. Stiller,[9] by Pel,[10] by Leyden,[11] by Jacobi and Lubilinski,[12] and by G. Leubuscher, it has been highly praised by Silvestrini[13] and by E. Maragliana.[14] E. Sansom[15] gives as the result of his experience that convallamarin is very useful in *mitral stenosis* with failing of the heart. Marmé found that the fatal dose of convallamarin was, for the dog, 0.015–0.03 gramme ; for the cat, 0.005 gramme ; for the rabbit, 0.006–0.008 gramme. Sée gives, of an aqueous extract of the whole plant, from fifteen to twenty-three grains a day ; Bojojawlewsky, each day an infusion representing from fifty to one hundred grains of the plant. The U. S. Pharmacopœia recognizes a fluid extract only (EXTRACTUM CONVALLARIÆ FLUIDUM), the dose of which is from five to fifteen minims (0.3–0.9 C.c.). The results obtained by Nathanson (see page 327) show that great caution must be exercised in the practical use of the active principles of convallaria.

SPARTEINE.

Sparteine is a liquid alkaloid obtained from the Cytisus Scoparius, or common broom plant. (See SCOPARIUS.) It is colorless, of a penetrating odor and extremely bitter taste, soluble in alcohol, in ether, and in chloroform. Sparteine sulphate (SPARTEINÆ SULPHAS, U. S.) occurs in colorless prismatic crystals or granular powder, freely soluble in water and in alcohol, having a neutral reaction and a bitter, slightly saline taste.*

PHYSIOLOGICAL ACTION.—According to Husemann,[1] Mitchell found about four grains of sparteine administered to the rabbit to cause a very short stage of excitation, followed by quiet sleep and death in three hours ; while in Schroff's experiments a single drop produced violent convulsions, followed by muscular weakness, depression of the heart's action, renewed convulsions, and death. The more recent researches of De Rymon, Griffe, and others show that there are two stages of sparteine-poisoning : the first of these is characterized by trembling, incoördination of movements, increase of reflexes, clonic and tonic convulsions, embarrassment of respiration, acceleration of the pulse, and enfeeblement of the heart ; the second, by enfeeblement of all the functions, the respiration becoming more and more depressed, and death preceded by convulsions occurring from paralysis of the respiratory centres. Fick found that by artificial respiration life may be prolonged for a very considerable period. According to Legris, sparteine in doses of twenty-five centigrammes has no perceptible influence upon the human brain or spinal cord, although doses of thirty centigrammes or over cause vertigo, headache, palpitations, and formications in the extremities. After forty centigrammes Garand noticed very

* The hydrochlorate of *oxysparteine*, an oxidation product from sparteine, is freely soluble in water, and has been used with asserted good results hypodermically by Von Oefele, in dose of six-tenths of a grain, as an active cardiac stimulant. See K. Hürthle (*Arch. f. Exper. Path. u. Pharm.*, 1892).

decided cardiac pain, with sensations of heat and redness of the face, and loss of power in the legs,—these symptoms commencing about twenty minutes after the ingestion of the alkaloid and reaching their maximum in four or five hours.

Nervous System.—The conclusions reached by experimental physiologists in regard to the action of sparteine upon the nervous system are so contradictory as to imply that different alkaloids have been used under one name. According to Fick[2] and Mitchell, sparteine has a distinct influence upon the cerebrum; and Fick, Gluzinski,[3] and other observers have found that the loss of reflex activity and the fatal arrest of respiration are of centric paralysis; whilst De Rymon,[4] Griffe,[5] and Gluzinski are in accord in affirming that neither the motor nor sensory nerves are affected. In this they are confirmed by Cerna, who even states that the local application of strong solutions has no sensible effect upon the nerves. On the other hand, Fick and Mitchell state that the motor nerves are attacked, and A. R. Cushny and S. A. Matthews[6] find that sparteine is closely related in its physiological action to conium, its chief influence being upon the peripheral motor nerve-endings in the muscle, whereby it causes a paralytic asphyxia.

Guinàrd and Geley[7] state that sparteine locally applied paralyzes the sensory nerves in the eye, and may even be substituted for cocaine in operations upon the eye.

Circulation.—Laborde[8] was the first to note that sparteine actively affects the heart, increasing in the frog and in the mammal both the amplitude and height of the pulse-wave. The subject has been further investigated by Griffe, Garand,[9] Masius,[10] Gluzinski,[11] Cerna,[12] and by A. R. Cushny and S. A. Matthews with results which are seemingly so discordant as to make their complete reconciliation at present almost impossible.

The effect of the alkaloid upon the pulse-rate in its fullest serial development appears to be a primary slowing, followed by an acceleration, which in turn gives way to a pronounced decrease below the normal. The size of the dose is a very potent factor in determining the action on the pulse-rate; thus, if a very large dose is given the pulse at once becomes slow and remains slow. Again, the slowing before acceleration of the pulse has not been noted by various observers, and probably occurs only after very small doses, and in some cases, according to the researches of Gluzinski, it is due to a primary excitement of the vagi nerve. Fick, Griffe, Garand, Masius, Gluzinski, and Cushny and Matthews are in accord in stating that the acceleration of the pulse is due to peripheral paralysis of the pneumogastric nerves, with its consequent withdrawal of inhibition, whilst it seems to be proved that the final slowing of the pulse is the outcome of a direct impulse of the sparteine upon the heart itself. Neither muscarine (Fick) nor atropine (Cushny and Matthews) prevents the action of sparteine upon the heart.

The important question whether sparteine ought or ought not to be

considered a stimulant to the circulation seems not yet to be finally answered; that there is after large doses a final fall of arterial pressure is demonstrated by the concordant testimony of all observers; as is also the fact that such fall of pressure may be an immediate result if the dose be sufficiently large, and is, in part at least, due to direct cardiac depression. Garand, Gluzinski, Pawlow, and Cerna all affirm as the result of their own experiments that there is a distinct primary stage of increased arterial pressure; and in the experiments of Cushny and Matthews such rise of pressure immediately followed the injection of five milligrammes of the alkaloid into the veins of rabbits and cats, whether they had or had not been paralyzed with curare or other drugs. According to Pawlow, this rise of blood-pressure is due chiefly to stimulation of the vaso-motor centres; whilst Cerna reached the conclusion that it is caused partly by an increased activity of the heart and partly by centric vaso-motor stimulation. Cerna compares the action of sparteine to that of digitalis. Cushny and Matthews conclude that sparteine is entirely apart from digitalis in that it does not prolong systole, but slows the pulse simply by increasing diastole; and in that it favors excessive dilatation of the heart, and in any dose is a sedative rather than a stimulant to the viscus. They find that in the mammal the rise of blood-pressure is very brief and does not occur when the drug is given by the stomach. They conclude that the rise is not due to any specific influence of the sparteine, but is called forth by local irritation. It should be remarked that even Cerna states that the rise of blood-pressure after the use of sparteine is not a constant phenomenon, and none of these researches seem to us to have been extensive enough to be conclusive; so that further studies are required to give us positive knowledge of the action of sparteine upon the circulation.

Muscles.—When applied locally to the muscles, sparteine has some influence in diminishing their excitability and prolonging the duration of the latent period (De Rymon, Griffe, and Gluzinski). But it does not destroy the functional activity of the muscles, even when brought in direct contact with them in a concentrated form, and its muscular influence is too feeble to be manifested in general poisoning.

Kidneys.—It is still doubtful whether sparteine does or does not fully represent the diuretic influence of scoparius. Griffe affirms that in his experiments upon rabbits it produced absolute decrease in the excretion of urine, and although some clinicians assert that it acts in man as a distinct diuretic, others affirm that any increased diuresis is secondary to the regulation of the circulation.

SUMMARY.—The exact action of sparteine upon the nervous system is not at present known. According to some observers, it distinctly depresses both the cerebrum and the spinal cord, causing death by centric paralysis of respiration; whilst, according to other experimenters, it is a motor-nerve paralyzant and arrests respiration periph-

erally. Upon the muscles its action is so feeble as to be in no way manifested after the ingestion of poisonous doses. The small dose may first slow the pulse by stimulating the pneumogastric nerve, but after a sufficient dose the pulse-rate is sooner or later increased by pneumogastric paralysis, to be later diminished by the direct action of the drug upon the heart itself. Sparteine produces a very large pulse-wave, with a rise of the arterial pressure after the small dose; this rise being, according to most experimenters, due to stimulation of the heart and of the vaso-motor centres, but according to some it is a merely temporary phenomenon, the result of peripheral irritation; further, the action of the alkaloid upon the heart is likened by experimenters to that of digitalis, but it is certainly different in that the very large dose positively depresses the heart; moreover, according to certain investigators, the action even of the small dose is essentially different from that of digitalis, in that the diastole alone is prolonged, and the tendency is to enlargement rather than to contraction of the heart. It is not at present positively ascertained that the alkaloid is a cardiac stimulant, but it is probable that it first stimulates and then depresses the viscus.

THERAPEUTICS.—The use of sparteine in diseases of the heart has been studied by a number of clinicians, notably Sée, Garand, Roland,[13] Voit,[14] J. M. Clarke,[15] Kurloff,[16] and Pawinski,[17] who are all in accord in affirming it to be of value in the treatment of cardiac affections, in which it slows the pulse and renders it more regular, increases diuresis, and is superior to most other cardiac remedies in its power of controlling general nervous excitement. Pawinski states that in pure *nervous palpitation* it exceeds digitalis in power and certainty in action, and that it is a valuable sedative in *hysteria*, *neurasthenia*, and allied conditions. Both Pawinski and Sée assert that it has a remarkable power of regulating the heart's action; the latter observer, indeed, affirms that no known remedy equals it for the purpose of making an irregular pulse regular. On the other hand, Pawinski warns against its use in cases in which the heart-muscle is believed to have undergone degeneration. Its action is a rapid one, the symptoms produced by it, according to Clarke, Sée, and others, developing in thirty minutes to an hour after its ingestion, and continuing for five or six hours. According to Clarke, these symptoms consist primarily of a marked retardation of the pulse, with increase of the force and of the arterial tension, the skin at the same time becoming red and moist, while the respiration, which is at first quickened, soon becomes slower and fuller than normal. In overdoses it is said to cause very high tension of the pulse, with sharp cutting or throbbing pains in the cardiac region, and sometimes nausea. It has been employed with asserted excellent results in all forms of *valvular disease*, in *asthma*, and especially in *functional cardiac* derangements. The very important statement made by Clarke, that it will control the pulse-rate and general symptoms in *Graves's disease*, receives some confirmation in the work of Pawinski and in our own experience. Some clinicians, notably Hans Leo,[18] and Hiero Stoessel,[19] have found sparteine, however, a very uncertain remedy. We

do not believe that for general purposes it nearly equals digitalis : in our own trials with it in organic cardiac cases the results have been very unsatisfactory. It may be valuable as a succedaneum to digitalis, and even as a substitute in neurotic cases. Pawinski gives 0.016 to 0.04 gramme three times a day, increasing gradually to 0.6 gramme during the twenty-four hours. The statements of Guinàrd and Geley, that sparteine may be used successfully externally like guaiacol for an antipyretic, are strongly contradicted by Lannois.[20] The sulphate (SPARTEINÆ SULPHAS, U. S.) may be used in pill or solution in commencing dose from one-quarter to one-half a grain, cautiously increased to two grains if required, and repeated every six to eight hours.

ADONIDIN.

Adonis vernalis, a plant of Northern Europe and Asia, contains a glucoside to which Cervello has given the name of *adonidin*. According to Cervello,[1] adonidin causes in the frog first increase in the force of the systolic contractions, then irregularity of rhythm with long diastolic pauses, and finally arrest in violent systole, the most characteristic phenomenon being the peristaltic movements which precede the cardiac arrest. According to H. A. Hare,[2] adonidin first increases and then slows the rate of the beat in the cut-out frog's heart, while its injection into the frog is followed by a period of slowing of the cardiac movements, with long diastolic pauses, succeeded by great increase of the pulse-rate, which in turn gives way to slow movement, ending in arrest. The heart, either within or without the body, stops in diastole. Although Cervello and also Guirlet[3] state that the heart is arrested in systole, Hare affirms that, whether the heart be isolated or *in situ*, the arrest is diastolic. The contradiction is not easily explained, unless it be through the observation of Guirlet, that in the rabbit he has seen the left ventricle in permanent systolic contraction, with the other cavities dilated and full of blood. The slowing of the pulse noted by Hare was found by him to be due to stimulation of the pneumogastrics, as it was prevented by their section. That the diastolic arrest was not merely an occasional phenomenon the result of excessive inhibition, as is sometimes seen from digitalis, was proved by its occurring after section of the vagi, as well as by the fact that galvanization of these nerves in the later stages of the poisoning failed to inhibit the heart, the nerves appearing to be paralyzed.

In Hare's experiments adonidin increased very distinctly the arterial pressure in the dog, while decreasing the pulse-rate. After large doses the first rise is followed by a marked fall of arterial pressure, with irregularity of the heart's action, and finally diastolic arrest. The experiments of Cervello and of Bubnow[4] are in accord with those of Hare in showing that the drug produces first rise and then fall of pressure. Hare found that in animals whose spinal cord had been previously cut, a rise of pressure followed the exhibition of adonidin, but was not so great as in the normal dog, so that it is possible that the drug acts as a stimulant

not only on the heart but also on the vaso-motor system. The first slowing of the pulse, according to Hare, is the result of stimulation of the inhibitory nerves, since it was prevented by their previous section, while the final fall of pressure is at least in part due to the vaso-motor palsy, since neither galvanization of the sciatic nerve nor asphyxia had any effect at a time when the heart had still considerable power.

THERAPEUTICS.—In 1879 Adonis vernalis was introduced to the medical world as a cardiac stimulant by Bubnow, a pupil of Botkin. Since then it has been tested by a number of physicians, with fairly concordant results. The general testimony is that its action in disease resembles that of digitalis, and that it is useful in the same class of cases. It is much more prompt than is digitalis, and Durand affirms that it has no cumulative tendency. There has been some difference of opinion in regard to its diuretic action, and whatever of such influence it has must be attributed to its action upon the circulation in the kidneys rather than to any marked direct power over the secreting structure. Durand asserts that it never produces disturbances of the alimentary canal, but Lublinski and Huchard have both seen it produce so much vomiting or diarrhœa as to require its withdrawal. In a case reported by Durand in which by mistake three grains of adonidin were given every half-hour, violent vomiting and diarrhœa were the most troublesome symptoms. Bubnow employed the infusion made from the whole herb four to eight parts in one hundred and eighty parts of water, and of this he administered a tablespoonful every two hours. Durand gives the dose of adonidin as 0.02 centigramme (one-third of a grain) every three or four hours.

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FAMILY II.—CARDIAC DEPRESSANTS.

THERE are certain drugs which are used by practitioners to decrease the activity of the circulation, and it is these which are here considered under the heading of *Cardiac Depressants*. Many, in fact all of them, possess other powers besides those which cause them to be considered under this caption, and none of them are in very close accord in these qualities. There is, however, a *general* resemblance in the action of such as are derived from the vegetable kingdom, in that they are all depressants to the motor nervous system and yet all produce convulsions. H. C. Wood[1] has made an especial experimental study of these convulsions, and has found that they are cerebral and not spinal, because they do not occur in any part of the body separated by section of the cord from cerebral influence. Further, they are probably due to disturbance of the circulation at the base of the brain, for the following reasons, the truth of each of which has been experimentally determined: first, lessening of the circulation at the base of the brain will cause convulsions; secondly, the convulsions produced by the cardiac depressants do not occur until the arterial pressure is reduced about one-half; thirdly, if the disturbance of the cerebral circulation be artificially increased by tying the carotids previous to poisoning, or in any other way, the convulsions come on sooner and are more violent; fourthly, in some animals the convulsions caused by arresting circulation at the base of the brain are feeble and ill-defined, while in others they are violent, and in species of the first order cardiac depressants produce but slight convulsions, while in species of the second order they cause violent convulsions.

The indications for the use of a cardiac depressant may be said to be increased arterial excitement, sthenic fevers, and severe local inflammations. In order that a rational selection of the various drugs may be made for any individual case, it is necessary to study how, in these various conditions, relief is afforded by an arterial sedative. When there is arterial excitement from irritation or excitement of the heart, the mode of relief is too obvious to need discussion. It is plain that in such a case a drug should be selected which simply depresses the heart's action and does nothing more. When there is severe inflammation, such as pneumonia, with high arterial tension, the effect desired is a lessening of the flow of blood to the part. A simple cardiac depressant may do this by lowering the force of the circulation, but a cardiac vaso-motor depressant is far more powerful. The blood-vessels of

the inflamed part are already dilated, and consequently attract blood, as it were, to the part. If the remedy dilates all the blood-vessels, this local attraction ceases, and blood is diverted from the inflamed tissue. It would appear from the experiments of Ludwig, Schiff, and others[2] that the blood-vessels of the body, after complete dilatation, are able to hold twice their normal amount of blood, and Golz (quoted by Fothergill[3]) found that the intestinal vessels by themselves were able to contain all the blood of the body. These facts show how by means of an arterial sedative, which paralyzes the vaso-motor centres, "we can bleed a man into his own blood-vessels," or, in other words, get much of the effect of a venesection by drawing blood from the diseased part.

ANTIMONY.

ANTIMONII OXIDUM—ANTIMONY OXIDE. U.S.

A grayish-white powder, almost insoluble in water. Its solution in the stomach is dependent upon the acid there present, and it should not be used internally,—although it is capable of producing all the effects of tartar emetic, for the preparation of which it was introduced into the Pharmacopœia. ANTIMONII SULPHIDUM, U. S., ANTIMONII SULPHIDUM PURIFICATUM, U. S., and ANTIMONIUM SULPHURATUM, U. S., are still more uncertain preparations, whose therapeutic use ought not to be encouraged.

ANTIMONII ET POTASSII TARTRAS—ANTIMONY AND POTASSIUM TARTRATE. U.S.

TARTAR EMETIC occurs in the form of a white powder, the result of the pulverization of transparent, colorless, slightly efflorescent crystals, which are most commonly rhombic octahedrons. Its taste is at first very slight, but after a time styptic and acrid. In some persons it blisters the tongue and lips after a few moments of contact. Tartar emetic is insoluble in absolute but soluble in dilute alcohol, soluble in from two to three parts of boiling water, and in seventeen parts of water at 59° F. It is incompatible with alkalies and with acids, including tannic acid and substances containing it.

PHYSIOLOGICAL ACTION.—*Local Action.*—Locally applied, tartar emetic is an irritant, acting upon some very delicate and susceptible skins in a very short time. In most instances, however, its continuous application for several days is necessary to produce any effect. At first there is simply a redness, accompanied by some burning pain and the eruption of small papules, which shortly become converted into vesicles and then into pustules. These are irregular in shape and size, varying from one-eighth of an inch to an inch and a half in diameter, and are very painful. Sometimes these pustules give rise to small sloughs, but generally, if the application be withdrawn, they simply give origin to superficial ulcers, which readily heal.

Absorption and Elimination.—Tartar emetic is very rapidly absorbed

in the gastro-intestinal tract, and elimination commences almost at once. The minute dose probably escapes from the system altogether through the kidneys, but the toxic dose is certainly thrown off with the secretions from the whole length of the gastro-intestinal tract, and probably also escapes with the saliva. The freedom with which it is eliminated, and the readiness with which it is detected chemically in the urine, make the saving of the urine imperative upon the practitioner in all cases of suspected poisoning.

General Action.—The only symptoms which are induced by small therapeutic doses (one-twelfth of a grain) of tartar emetic when exhibited for a short time are a scarcely perceptible diminution of the force of the pulse and an increase of the perspiration. By somewhat larger amounts of the drug nausea is induced, accompanied in a more decided degree by the phenomena just mentioned. After large doses, prolonged nausea, violent vomiting and retching, with marked reduction of the force of the pulse, great muscular relaxation, and a feeling of faintness, occur. At the same time the saliva is generally increased in amount and the skin is bedewed with sweat.

After poisonous doses all these symptoms are intensified. The vomiting is violent, repeated, continuously re-excited by the slightest provocation, and is accompanied by burning in the œsophagus and stomach and by colicky pains in the abdomen. The matters vomited are first mucus, then mucus with bile, and finally, in some cases, blood. With the gastric disturbance occurs violent and frequent serous purging, the discharges resembling those of cholera, but becoming in some cases towards the last bloody. Cramps may occur in the extremities, and, in conjunction with the serous purging, have caused the antimonial poisoning to be mistaken for cholera. The exhaustion is extreme, and deepens into collapse, with thready or imperceptible pulse, pinched, livid countenance, suppressed voice, profuse cold sweats, lowered temperature, and at last death from asthenia, generally preceded by stupor or convulsions: indeed, Taylor reports cases in which wild delirium was present some hours before death. The urine * in mild cases is increased in quantity, as it is also in the beginning even in fatal cases, but in such towards the close it is generally scanty and bloody, and even suppressed. Upon the lower mammals tartar emetic acts precisely as it does on man.

Circulation.—In man and in all mammals any dose of tartar emetic which is sufficient to affect the circulation produces a steady fall of the arterial pressure, with a pulse-rate which may be at first slowed but soon becomes more rapid than the normal.

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* What is said in the text is, we think, correct, although authorities differ on this point. Trousseau (*Traité de Thérapeutique*, 4th ed., i. 619) affirms that it is suppressed; Husemann, that it *never* is suppressed (*Toxicologie*, 854); Tardieu, that it is scanty. For a case in which it *was* suppressed, see Taylor's *Medical Jurisprudence*, London, 1873, 309. C. Gäthgens (*Centralbl. f. Med. Wiss.*, 1870, 321) found, in some incomplete experiments, an increase of the elimination of urea after repeated non-toxic doses of antimony.

In the lower animals all doses of antimony sufficient to cause any apparent effect progressively lower the arterial pressure; the pulse is sometimes at first temporarily accelerated, but usually the slowing of the pulse occurs from the beginning of the poisoning. During this period of slow pulse the diastolic pauses are extremely long and the pulse-waves greatly augmented, it may be to five times their original size. After a time the pulse usually becomes very rapid, the pulse-waves very small, the arterial pressure almost extinguished, and in a few minutes diastolic arrest occurs (Ackermann,[1] Ernst Sentz[2]). In the poisoned frog the cardiac contractions are from the beginning lessened in frequency and force, then become more rapid but extremely irregular, with the auricles pulsating more frequently than the ventricles (Radziejewski,[3] Ackermann, Nöbiling[4]). The peripheral vagi are paralyzed so that the diastolic arrest is not inhibitory (Radziejewski). Antimony paralyzes the isolated frog's heart, destroying the irritability of the muscle (Ackermann); digitalis is stated to produce immediate restoration of function (I. Soloweitschyk[5]).

Antimony is certainly a direct cardiac depressant and paralyzant, but the assertion of Soloweitschyk that galvanization of the vaso-motor centre does not elevate the arterial pressure whilst the heart is still active, taken together with the fact that the arterial pressure falls whilst the heart is apparently putting forth its normal force, indicates that the poison also depresses either centrically or peripherally the blood-vessel system.

Nervous System.—The occurrence in man of anæsthesia during antimonial poisoning has been overlooked, but has been a marked feature in experimental poisonings. According to Radziejewski, the thermic sense is first paralyzed and later the tactile power. Radziejewski and Soloweitschyk have found that the depression of reflex activity occurs after, as before, section of the cord, and is therefore not due to stimulation of the Setschenow inhibitory centre; also that it is not prevented by tying an artery and cutting off access of the poison to the nerve, and is therefore not peripheral. It consequently must be spinal; and, as both observers noted that in the frog and the rabbit voluntary movements persist after the total abolition of sensibility and reflex activity, antimony must be a paralyzant of the *receptive centres or sensory tract of the spinal cord.* The motor cord probably shares to a slight extent in the depressing influence. The motor nerves and muscles are said to retain their functional power.

Temperature.—The influence of antimony upon the temperature appears not to be very marked when the drug is exhibited in ordinary therapeutic doses. Ackermann affirms that, after doses severe enough to induce violent vomiting, the centric temperature is not lowered, although that of the extremities may fall as much as 3.5° C. After poisonous doses of antimony the decrease of animal heat is very perceptible.*

Abdominal Organs.—Tartar emetic acts as an irritant upon the whole alimentary mucous membrane. The serous discharges from the stomach and from the bowels may be to a certain degree due to the local irritant influence of the poison, but probably to a much larger degree are the outcome of an attempt to eliminate the drug circulating in the blood.

* Ackermann found that a fall of only 1.6° C. occurred in rabbits killed in an hour, but in those that lived five hours the depression amounted to 6.6° C.

Brinton proved that when tartar emetic was injected into the vein of an animal it was very freely and rapidly eliminated by the stomach. B. W. Richardson [6] has corroborated this, and has also found that a similar elimination follows the inhalation of antimonietted hydrogen. Radziejewski's theory that the emesis is due solely to a local action of the poison is completely disproved by the experiments of Magendie (confirmed by Brinton [7]), in which vomiting was produced by tartar emetic after the stomach had been removed and a pig's bladder substituted. The vomiting caused by tartar emetic must therefore be, at least in part, of centric origin, but Mosso [8] has proved that the local action of the drug also plays an important *rôle* in the production of vomiting; finding that when the tartar emetic is given by the mouth, vomiting is caused by smaller quantities and more promptly than when the poison is injected into the veins.

Respiratory Organs.—The respiration in poisoning by antimony is very irregular, with all sorts of variations in the rhythm of the act, and is probably centrally depressed.

In the advanced stages the pauses are often very long, and the inspiration and expiration so forced and prolonged that very generally, in animals at least, marginal emphysema and subpleural ecchymoses are found after death. The origin of the respiratory trouble is probably somewhat complex, the chief factor being the direct influence of the drug upon the respiratory nerve-centres, and minor causes the intense venous congestion due to the failure of the circulation and the alteration of the blood itself.

Upon the mucous membrane of the lungs antimony acts directly or indirectly, even in moderate doses, as is shown by clinical experience and by the experiments of Mayerhofer.[9]

SUMMARY.—Locally, tartar emetic is a violent irritant, which is rapidly absorbed and rapidly eliminated through the kidneys, and also, when the dose has been large, through the mucous membranes of the whole gastro-intestinal tract, causing during the process of elimination violent inflammation and it may be destruction of the eliminating tissues. It is a powerful depressant to the circulation, acting directly upon the heart-muscle or its contained ganglia, and also widening out blood-paths by paralyzing the vessels, whether centrically or peripherally is not known. By the toxic dose the peripheral vagi are depressed and finally paralyzed. The vomiting produced by tartar emetic is in part due to the local action of the drug upon the stomach, but is chiefly centric. The largest therapeutic dose has no perceptible direct action upon the nervous system, but the toxic dose depresses the respiratory centres, the receptive or sensory centres of the spinal cord, and finally the motor cord,—the nerves and the voluntary muscles retaining their functional power. Tartar emetic kills by producing exhaustion and by paralyzing the respiratory centres and also the heart.

THERAPEUTICS.—There are three indications to meet which tartar emetic is constantly employed. The first of these it fulfils by virtue of its powers as an emetic. The discussion of this may be found in the chapter upon Emetics.

The second purpose for which antimony is used is to *depress arterial excitement.* It is chiefly in *inflammation* that tartar emetic is used as an arterial sedative. In combination with more decided diaphoretics it is

constantly employed by some surgeons in *gonorrhœa* and in various sthenic inflammatory affections. In *pneumonia* it has been very largely used, forming an essential portion of the old so-called contra-stimulant plan of treating that disease. According to the method of Rasori, four or five grains a day were at first given, but rapidly increased to twenty-four or even thirty grains daily. Although by the aid of opiates and careful dilution a species of tolerance was often obtained for these heroic doses, the method has very properly been abandoned by modern therapeutists. Whenever tartar emetic is given in such quantities as markedly to depress the circulation by the vomiting and purging which it causes, it produces in the patient exhaustion as well as depression. Further, by the continuance of its local influence upon the intestinal tract after the period of depression, it interferes with the digestion of food and consequently with the regaining of power. On the contrary, neither aconite nor veratrum directly exhausts, though they powerfully depress. They are, therefore, always preferable to tartar emetic when in a pneumonia or other disease it is desired to produce a temporary pronounced depression of the circulation. In fact, tartar emetic should never be employed as an active depressant of the circulation.

Owing to its action upon the mucous membrane of the bronchial tubes, in the first stages of *bronchitis* tartar emetic is a valuable remedy. After free secretion has been established, other expectorants are, we think, of more service. It should be used only in sthenic cases, and never, unless in the most minute dose, in children or the aged.

As a *counter-irritant*, tartar emetic is used only when it is desired to produce a slow, persistent, and at the same time very decided impression. For further discussion of its application to disease, see the chapter on Rubefacients.

Toxicology.—The symptoms ordinarily produced by poisonous doses of antimony have been sufficiently described. There is, however, according to authors, a form of antimonial poisoning in which neither vomiting nor purging * occurs, the symptoms being simply intense prostration, cold clammy sweat, a sense of oppression in the chest, with the respiration at first increased, then diminished in frequency and embarrassed ; a rapid feeble pulse, after a time becoming slow, intermittent, and irregular ; delirium, unconsciousness, tremblings, and clonic and tonic convulsions (Husemann[10]). Tardieu states that in some cases of tartar emetic poisoning a rash exactly resembling that produced by the external application of the drug has appeared all over the body on the fourth or fifth day.

The lesions of gastro-enteritis which are usually found after death from tartar emetic are sometimes not present.† The venous system is

* Husemann states this. Although vomiting is absent in these cases, purging is generally present. We do not remember to have seen the report of a case in which it was absent.

† For cases, see *Archives Gén.*, Sept. 1865.

generally very much engorged, and the viscera are intensely congested. Magendie asserted that in animals poisoned by tartar emetic the lungs are always full of portions apparently hepatized; but Ackermann, in twenty experiments, found only some marginal emphysema and subpleural ecchymoses, with, in one or two cases, spots of atelectasis in the lungs. The assertion of Magendie, therefore, is too sweeping; but it is true that, in a large proportion of fatal cases of antimonial poisoning, emphysema, pulmonary apoplexy, atelectasis, or other structural lesions of the lungs exist. The blood usually coagulates imperfectly.

Salkowsky,[11] of Moscow, has found that when animals are fed upon antimonic acid (one-half to one gramme daily) or other preparations of the metal for from fourteen to nineteen days, the liver, kidneys, and even the heart undergo fatty degeneration; also that there is a lessening of the amount of glycogen in the liver, and in some cases even a total disappearance of it. This has been confirmed by Grohe and Mosler, who state that in the duchy of Brunswick the peasantry give to the geese, when producing the famous fatty livers, a certain quantity of the white antimony oxide every day.

The minimum fatal dose of tartar emetic is not known. Three-quarters of a grain in a child, and two grains in an adult, have proved fatal, but in the latter case extrinsic circumstances favored the result (Taylor,[12] an analysis of thirty-seven fatal cases); two hundred grains have been recovered from;[13] also one hundred and seventy grains.[14]

The treatment of antimonial poisoning consists in washing out the alimentary canal with large draughts of *tannic acid*,—the best known antidote,—in the free administration of opium by the mouth or rectum, or hypodermically if it cannot be retained, the hypodermic injections of strychnine and digitalis if the circulation fails, and the maintenance of the bodily temperature by external application of heat.

Chronic Poisoning.—The symptoms following the criminal repeated administration of small toxic doses of tartar emetic at intervals are nausea, mucous and bilious vomiting, watery purging, often followed by constipation, small frequent pulse, and asthenia, deepening into death from exhaustion.

ADMINISTRATION.—The sudorific dose of tartar emetic is one-twelfth of a grain (0.0054 Gm.), the emetic dose one-half to one grain (0.032–0.065 Gm.), repeated every twenty minutes as necessary. Antimonial Wine (VINUM ANTIMONII, U. S.), about two grains to one fluidounce; full emetic dose half a fluidounce (15 C.c.). An ointment (twenty per cent.) has been used as a pustulating counter-irritant. A small quantity is spread upon a linen rag and laid upon the skin, or a little of it may be well rubbed in twice a day. The effects are severe and persistent.

VERATRUM VIRIDE. U.S.

The rhizome and roots of Veratrum viride, a coarse perennial herbal plant, indigenous to the Northern United States. It is a large tapering

rhizome, an inch or two in length, less than an inch in thickness at the base, and having a bitter acrid taste.

The nature of the active principle of veratrum viride has been the subject of much investigation and discussion by chemists, the results of which are given in full in the eighteenth edition of the U. S. Dispensatory. Suffice it for the present to state that the later researches seem to show that in veratrum viride there exist six alkaloids instead of two as formerly believed. The most important of these alkaloids are *jervine* and *rubijervine;* the others—*pseudojervine*, *cevadine*, *veratrine*, and *veratralbine*—are present only in very minute quantities; rubijervine is the *veratroidine* of Charles Bullock.

Local Action.—Veratrum viride is not actively irritant, although there is reason for believing that the vomiting which it causes is partly due to some local influence exerted by it upon the stomach. It yields its active principle very rapidly to absorption; its effects become apparent in fifteen to twenty-five minutes after its ingestion. Concerning its elimination we have no practical knowledge, but its active principle probably escapes through the urine.

General Action.—The only effect perceptible in man after the small physiological dose of veratrum viride is a reduction of the force of the pulse. If the dose has been a little larger the pulse frequency also falls very markedly, it may be to 40 or even 30 per minute. The volume of the pulse rises, though the force of it is very slight. The final reduction of the pulse-rate is accompanied by nausea, and at last by vomiting, which becomes after a very large dose exceedingly severe. By exercise this slow, large, soft pulse may be converted into a rapid, very feeble and small pulse. Under any circumstances the rapid pulse develops sooner or later if the dose has been sufficient, and is accompanied by intense muscular weakness and great sweating. Finally, there are a running, almost imperceptible pulse; a cold, clammy skin; intense nausea, and incessant attempts at vomiting, or retching, or hiccough; absolute muscular prostration; faintness; vertigo; loss of vision; and semi-unconsciousness. Various observers also speak of an excruciating præcordial pain; but this we have not seen. The intestines are usually not disturbed, but severe purging has been noted.

In 1870 H. C. Wood[1] made an elaborate study of the alkaloids jervine and veratroidine (rubijervine) supplied to him by Charles Bullock, with results which are here epitomized.

In the dog and rabbit jervine caused sluggishness, with progressive muscular weakness and diminution of the reflexes; with, after a time, violent general tremors ending in convulsions in which, although the movements were violent, there was evident loss of power. The pupils were not affected; there was no purging or vomiting, though always profuse salivation. Locally, jervine was not irritant. Consciousness was preserved almost to the last, and death occurred from asphyxia. Physiological studies showed that the convulsions were of cerebral origin, but were probably due to disturbances of circulation in the brain, the brain not being other-

wise affected; also that the loss of muscular power was due to spinal depression, the function of the peripheral nerves and the muscles not being interfered with.

Upon the respiratory centres jervine acted as a direct depressant, but its influence upon the circulation was not at all subordinate to its action upon the respiration, and when final arrest of respiration occurred the circulatory forces were almost abolished. The circulatory phenomena were primary slowing of the pulse, with later rapid pulse, and a progressive falling of the arterial pressure from the beginning to the end. The slowing of the pulse was not due to any effect on the pneumogastric nerves, the jervine acting as usual after section of these nerves, and galvanization of the nerves producing the ordinary results in the deeply poisoned animal. The slowing of the pulse was due to a direct influence upon the heart-muscle or its ganglia, which is depressed by any dose of the poison. As, however, neither asphyxia nor galvanization of a sensory nerve produces rise of pressure in the poisoned animal, it is evident that jervine depresses the vaso-motor centres.

The physiological action of jervine may be summed up as that of a powerful depressant of the heart and of the vaso-motor centres, which acts also upon the motor side of the spinal cord and upon the respiratory centre, but has little other influence upon the organism.

Veratroidine was found to be more irritant than jervine, producing usually vomiting and sometimes purging, but not causing such severe convulsions as did jervine, death taking place from central asphyxia. In its relations with the cerebrum, the spinal cord, the peripheral nerves, and the muscles veratroidine practically acted like jervine. The circulatory action of veratroidine was entirely subordinate to its influence on the respiration, so that when given in toxic dose hypodermically it caused an enormous rise of the arterial pressure, due to the rapidly induced centric asphyxia, as was shown by the fact that it did not occur when artificial respiration was maintained. After section of the par vagum, veratroidine was powerless to reduce the pulse-rate, and division of the par vagum in the poisoned animal was followed by an enormous rise in the pulse-rate. Further, it was found possible to cause by the intravenous administration of a certain dose of veratroidine, artificial respiration being maintained, a diastolic arrest of the heart's action, which was at once relieved by division of the par vagum or by a second injection of the poison; so that an animal apparently dead could be restored to life by vagal section or by giving more of the poison. As it was proved that the large dose of veratroidine paralyzes the peripheral vagi, it is evident that the diastolic arrest just spoken of was due to excessive cardiac inhibition, and that its removal by section with the knife, or with the drug, allowed the heart to go on.

During the period of low pressure, galvanization of the sensitive nerve, or asphyxia, produced an immediate rise in the arterial pressure, conclusive proof that the vaso-motor centres were not affected.

These effects upon the circulation were obtained only when artificial respiration was maintained, the effect of the drug upon the respiratory centre being so intense that when the animal is left to itself death occurs before any very direct influence has been exerted upon the circulation.

Veratroidine is, therefore, a powerful respiratory poison, lessening at first the frequency of the cardiac beat by stimulating the pneumogastrics, but soon losing all power over the heart, owing to the powerful influences of the asphyxia produced by it.

The action of veratrum viride is the result of the combined influence of its alkaloids, and as the relative proportions of these alkaloids differ in

different rhizomes, so in the finer details of its physiological action one specimen of veratrum viride differs from another. For all practical purposes, however, its influence is uniform, and may be summed up as follows:

SUMMARY.—Veratrum viride has no distinct local action, yields readily its active principles to absorption and probably to elimination, though concerning its fate in the system we have no definite information. The free sweating which accompanies its marked action may be simply the result of a profound arterial depression, there being no proof that the drug exerts a specific influence upon the glands of the skin. Similarly the excessive secretion of bile which it sometimes induces may be a secondary result due to the severe vomiting.

By the depressing action of jervine upon the heart-muscle and upon the vaso-motor centres, veratrum viride lowers the arterial pressure, in the beginning slowing the pulse by a direct influence of jervine upon the heart-muscle, and by the stimulating influence of veratroidine upon the pneumogastric nerve, but later increasing the rapidity of the pulse by paralyzing the pneumogastric nerve (veratroidine), and probably also by some action upon the heart-muscle (jervine). Chiefly, if not solely, through a centric influence, it causes violent vomiting, and in rare cases, when there is in it an excess of the veratroidine, purging. On the motor side of the spinal cord it acts as a powerful depressant, but is without influence upon the cerebrum, the motor nerves, and the muscles. Probably, on account of the vaso-motor paralysis which it produces favoring an increase of heat-dissipation, it decidedly lowers animal temperature, a fall of as much as four or even more degrees sometimes occurring in the poisoned lower animals before death.

THERAPEUTICS.—With our present knowledge of the physiological action of veratrum viride, it is evident that there are only two rational indications for its use,—namely, to *reduce spinal action* and to *reduce arterial action*. Owing to the very great effect veratrum viride has upon the circulation, and to the numerous drugs which are purer spinal depressants, it is rarely called on to meet the first indication, and in practice should simply be used to lessen the force of the circulation. The use of the drug in *typhoid fever* and other adynamic diseases is simply an irrational and dangerous practice, founded upon an erroneous idea of the action of the remedy.

Veratrum viride has been recommended in *mania a potu;* and in cases of irritation of the brain from drink, with strong bounding pulse, it may be of great service; but in the true *delirium tremens*, with universal adynamia, it is a thoroughly improper remedy, capable of deepening the prostration into fatal exhaustion; indeed, we have known of death occurring in this disease from its use.

When true sthenic arterial excitement is to be combated in any disease, except it be *gastritis*, veratrum viride may be employed as a prompt, thoroughly efficient, and at the same time very safe remedy,—very safe, since it is almost incapable of producing death in the robust adult, unless used with great recklessness and in repeated doses. In the early stages

of *sthenic pneumonia* it offers, we believe, the best known method of reducing the pulse-rate and the temperature, and of lessening the congestion.* It is hardly necessary to mention other individual diseases in which veratrum viride may be employed to carry out the present indication. In *peritonitis* its tendency to cause vomiting is very much against its use, and, unless this action can be controlled, should interdict its employment.

In chronic *cardiac diseases* it may be used in precisely those cases in which digitalis is contra-indicated,—*i.e.*, where there is excessive hypertrophy ; but, on account of its less persistent influence and greater tendency to disturb digestion, it is usually less advantageous than is aconite.

The contra-indications to the use of veratrum viride are cardiac weakness and the existence of general adynamia. As an emetic, veratrum viride should never be employed.

Toxicology.—Although veratrum viride is a remedy of great power, capable of producing the most alarming symptoms, yet it is the safest of the cardiac depressants. Overdoses of it provoke vomiting so soon and so certainly that it is somewhat doubtful whether a robust adult could be killed by a single dose of any of its official preparations, especially if prompt and judicious treatment were afforded.

We have several times known a teaspoonful of its fluid extract to be taken, and Percy cites recoveries after the ingestion of a tumblerful of the tincture ; after thirty grains of the resinoid ; after two doses—a tumblerful each—of a syrup representing a pound of the root to the pint. A feeble child, eighteen months old, was killed by thirty-five drops of the tincture,[2] and a doubtful case of fatal poisoning in the adult is mentioned.[3] J. D. Blake[4] reports a death resulting from the administration of between three and four drops of Norwood's tincture every two hours to a babe eleven months old ; and a man convalescing from typhoid fever was killed by a drachm of the fluid extract.[5]

In cases of poisoning, vomiting should be encouraged by large draughts of warm water until the stomach is well washed out. Then the patient should be forced to lie flat upon the back, with the head lower than the feet, and the efforts at vomiting should be restrained. If they cannot be checked, and if the prostration be severe, on no account should the patient be allowed to rise up, but must be made to vomit into a towel. A full dose of laudanum should be given by the rectum, and brandy or whiskey be administered by the mouth. Tincture of digitalis and strychnine should be given hypodermically. We have noticed that spirits will sometimes be retained only when given undiluted, and in such form will quiet the stomach at once. If the stomach refuses alcohol in any shape, the rectum should be made use of. Ammonia may be employed as an adjuvant to alcohol. External heat is important, and mild flagellations, rubbing with coarse towels, sinapisms, etc., may be used to keep up the external capillary circulation.

* Compare Oulmont (*Bulletin de Thérapeutique*, lxxiv. 146) and Zuber and H. Hirtz (*Ibid.*, lxxvi. 468).

ADMINISTRATION.—In administering veratrum viride, it should always be borne in mind that it will do no good in acute disease unless given in increasing doses until its physiological action is manifested.

In almost all cases vomiting is to be avoided as far as possible. To do this, small quantities of the drug may in some cases be given at short intervals, and corresponding doses of laudanum (five to ten drops) should be exhibited fifteen minutes before each dose of veratrum viride. An hour is generally the best interval between the doses.

Dose of fluid extract (EXTRACTUM VERATRI VIRIDIS FLUIDUM, U. S.), one to three minims (0.06–0.18 C.c.); of tincture (TINCTURA VERATRI VIRIDIS—forty per cent., U. S.), three to six minims (0.18–0.36 C.c.).*

VERATRINA. U. S.

This alkaloid is procured from the seeds of Veratrum Sabadilla (Asagræa officinalis †). As found in commerce, it is almost always more or less impure, and occurs as a grayish-white powder of an intensely acrid taste, and producing, even in the minutest quantity, when smelled, frequently repeated sneezing, which may continue for hours.

PHYSIOLOGICAL ACTION.—Veratrine is exceedingly irritating to any surface it may come in contact with, producing when given hypodermically or endermically severe pain, and when rubbed on the skin a feeling of warmth, followed by prickling, severe pain, numbness, and, if its use be persisted in, a marked redness. On the mucous membranes its action is even more decided. In the nostrils the minutest portion of it produces intense irritation, as shown by repeated sneezing and free discharge, which may be bloody. Upon the tongue a speck causes burning, with free salivation. When taken internally, in small doses, it causes

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* VERATRUM ALBUM—*White Hellebore.*—The *Veratrum album* of Europe and the *Veratrum viride* of America appear to be one species. Differences in soil and climate produce differences in the proportion of the various alkaloids in the rhizomes, so that the action of neither American nor European samples is always consistent. Usually, however, the irritant alkaloid is more abundant in *V. album* than in *V. viride*, so that the symptoms of white hellebore poisoning, as usually recorded, are similar to those caused by the green hellebore, with the addition of severe abdominal pain and violent diarrhœa, and with the further difference that poisoning by Veratrum album is much more apt to end in death than by Veratrum viride. A careful examination of the records shows, however, that Veratrum viride poisoning sometimes has taken on the features usually attributed to Veratrum album poisoning, and that violent abdominal pain and purgation are not constant in Veratrum album poisoning. (See H. C. Wood and H. C. Wood, Jr., *Amer. Journ. Med. Sci.*, May, 1899.) Further, a careful physiological study of the two drugs shows that their influence is practically the same upon the respiration and the circulation.

Veratrum album is not used at all in American medicine; from its greater tendency to purge, it is inferior to Veratrum viride, but may be employed for the same purposes and in the same doses as Veratrum viride. The treatment of its poisoning is that of Veratrum viride poisoning, with the freer use of opium when there is great intestinal disturbances.

† The action of *sabadilline*, the congeneric alkaloid of veratrine, has been partially studied by I. Urpav (*Montpellier Méd.*, 1883, i. 274), who finds it to have only about one-twelfth the toxic power of veratrine.

slowing and weakening of the pulse; more freely administered, indications of gastro-intestinal irritation; and in large doses it is followed by violent vomiting, serous purging, often with intense burning in the mouth and throat, and general muscular weakness. No fatal case of poisoning is on record;* but in the experiments of Esche on himself a half-grain of the acetate produced collapse, with a pale, cold, wet skin, pinched features, a rapid, thready, irregular pulse, violent vomiting, and marked muscular tremblings. Other observers have noted more pronounced indications of convulsions; and, according to Bardsley, when absorbed through the skin, instead of purging it produces in some cases very free diuresis.

Although official, veratrine is almost never used in practical medicine, and we therefore merely epitomize our knowledge of its physiological action, referring the reader to the tenth edition of this treatise for its more elaborate study.

Veratrine is primarily a muscle-poison.

When a muscle during the convulsive stage of veratrine-poisoning is momentarily stimulated, instead of the usual momentary contraction a prolonged tetanic spasm results and lasts some seconds: this spasm is induced by the slightest irritation. When the supplying nerve is irritated repeatedly within a short time, the muscle loses its power of entering upon a "veratrine contraction," but if left quiet for a time recovers itself. There is, therefore, in veratrine-poisoning, preceding the stage of muscular paralysis, a stage of muscular hyperexcitability. It can scarcely be doubted that this is the result of an action not upon the nerve-endings, but upon the sarcolemma of the muscle.† Finally, if the dose of veratrine has been large enough, the muscle becomes contracted, stiff, fails to respond to any irritant whatever, and exhibits the acid reaction of post-mortem rigidity.

On the cerebrum veratrine has probably little action.

It is impossible at present to reconcile the discord of investigators as to the influence of the drug upon the spinal cord. It is probable that it acts directly as a paralyzant on both motor and sensory nerves. It is a powerful depressant to the respiratory centre, killing chiefly by the production of asphyxia, and acts upon the heart-muscle and probably upon the muscles in the coats of the arteries as upon voluntary muscles; in the beginning, by its influence on the heart and arteries, it temporarily in-

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* In *St. George's Hospital Reports*, 1870, v., C. Paget Blake reports a case of recovery after the ingestion of a liniment supposed to contain three grains of veratrine! Intense itching of the skin was a prominent symptom.

† Fick and Boehm believe that they prove that the prolongation of the muscular contractions in veratrine-poisoning is due to a greater intensity of the chemical processes of the muscles, and not to a delay of the process of restitution. A discussion of this point would involve that of muscular physiology, and cannot be entered into here. The weak point of the argument made by Fick and Boehm may, however, be pointed out. Granting all their asserted facts, it is perfectly possible that greater intensity of the chemical processes is an *effect*, not a *cause*, of the prolonged contractions.

creases the blood-pressure, but soon lowers it, the pulse being in the early stages of the poisoning slowed, largely by the stimulant influence upon the inhibitory apparatus.

THERAPEUTIC ACTION.—Veratrine was formerly recommended in *acute rheumatism* and in *dropsy*, but with the growth of the modern materia medica this employment of it is unjustifiable. It is sometimes used as an irritant applied to the spine and to the skin of the affected muscle in certain *palsies*, and the U. S. Pharmacopœia recognizes an ointment (1 to 25) for this purpose and for use in *neuralgia*. One-sixteenth of a grain of veratrine has produced most alarming symptoms. It is absorbed readily through the skin, and, even if used externally, is a more dangerous than useful remedy.

ARNICÆ FLORES—ARNICA FLOWERS. U.S.
ARNICÆ RADIX—ARNICA ROOT. U.S.*

The flower-heads, rhizome, and roots of the Arnica montana, a perennial composite, native of Northern Europe and Asia, and said also to be found in the Northwestern United States. The yellow flowers have about fourteen striated ligulate tridentate florets in the ray, twice as long as the disk, which consists of numerous tubular florets. Of its two alkaloids, *arnicine* and *cytisine*,† the latter is said to be identical with the active principle of the laburnum (*Cytisus laburnum*).

PHYSIOLOGICAL ACTION.—Locally, arnica is stimulating, and, if in sufficient strength, decidedly irritating. Upon some skins the tincture acts even violently, rapidly developing an acute eczematous inflammation of the upper dermal layers, as manifested by hyperæmia, papules, vesicles, excoriations, crusts, and scales in regular sequence.[1]

Neither the symptoms of poisoning by arnica nor its physiological action are well made out.

According to H. A. Hare,[2] the fluid extract in doses of five to ten drops produces in the dog a slowing of the cardiac beats, with increase of the fulness of the pulse-wave and a very slight increase of the arterial pressure, the slowing of the pulse being the result of a stimulation of the pneumogastric nerves, and the slight increase of the arterial pressure probably caused by increased heart-work. After large doses the pulse becomes very rapid, from pneumogastric paralysis, the arterial pressure remaining near the normal. Viborg (quoted by Stillé) affirms that in horses and cows it causes increased action of the heart, flow of urine, and warmth of skin, followed by very decided general depression.

According to Stillé, the effects of moderate doses on man are similar to those noted as occurring in the lower animals,—namely, increase of the cardiac action, of the respiration, of the temperature of the skin,

* This drug probably does not belong in the present class.

† J. L. Prevost and Paul Binet find that *cytisine* is a powerful centric emetic, which in large doses paralyzes the motor nerves. Its direct action upon the circulation is very slight; toxic doses cause a gradual lowering of arterial pressure and death by respiratory paralysis (*Revue Méd. de la Suisse Rom.*, vii. and viii., 1887; see also R. Radziwillowicz, *Thesis*, Dorpat, 1887).

inches long, very tapering, about three-quarters of an inch in diameter at the base. Its taste is bitterish, acrid, and after a little while benumbing, giving origin to intense tingling of the lips and mouth. It is to be distinguished from horseradish root, with which it has been sometimes fatally confounded, by its external brown color and its lack of odor when scraped. The whole plant is active and tastes like the root.

In 1833 Geiger and Hesse discovered in aconite the alkaloid *aconitine*. According to the most recent researches, there are in the rhizome, however, besides aconitine, two alkaloids, *benzaconine* and *aconine*, which may also be made by the hydrolysis of aconitine, benzaconine being the *isaconitine*, and the principal constituents of the *napelline* and the *picraconitine* of older writers (Cash and Dunstan [1]).

Aconitine of commerce is a more or less impure mixture of several alkaloids. It is not recognized by the U. S. Pharmacopœia, but is by the British. As neither the constitution nor the composition of pure aconitine has been established by chemists, it seems doubtful whether the result of even the most recent researches should be accepted as final.

PHYSIOLOGICAL ACTION.—*Local Action.*—Aconite and aconitine are locally irritant, but this irritant influence is soon overwhelmed by the effect of the drug upon the peripheral ends of the sensory nerves, so that numbness and tingling are produced at the point of application. Moreover, the general influence of the drug is so overwhelming that the local effect counts for very little in practical medicine.

Absorption and Elimination.—Aconite yields its alkaloids with great rapidity to absorption, and aconitine is capable of passing through the mucous membranes and even the skin, making it in pure form a dangerous external remedy. Concerning its elimination we have no knowledge.

General Action.—The symptoms which are induced by small therapeutic doses of aconite in man are reduction of the force and frequency of the circulation, a sense of muscular inertia and weakness, and a slight tingling in the extremities or in the lips. If the dose administered be large, all these symptoms are intensified; the muscular weakness is extreme; the tingling is felt all over the body; the pulse is feeble, and reduced to 30 or 40 per minute; the respirations are diminished; giddiness and disordered vision may be manifested, especially when the erect posture is assumed. After three or four hours these symptoms gradually subside.

When a poisonous dose has been ingested, the first thing noticed in most cases is a burning or tingling in the throat or in the extremities, soon spreading over the whole body. The pulse rapidly falls in frequency, and in a very little time becomes exceedingly weak, intermittent, irregular, and finally imperceptible; the muscular strength is greatly reduced and sometimes almost entirely gone; the respirations are shallow, feeble, irregular, and infrequent; the general sensibility is very much benumbed, so that marked anæsthesia of the surface is present; the skin is bedewed with a cold sweat; the countenance is anxious,

sunken, livid, and the eyes are often protruded, or are even spoken of as glaring; the pupil is generally dilated, but when there are no convulsions may be contracted; gastric burning is sometimes complained of, and severe vomiting may be present, but the stomach is not rarely retentive. The intellect generally remains unaffected until very near the close, sometimes to the very moment of death.* In the collapse of the latter stages of aconite-poisoning the special senses may be lost, especially the sight. The voice is very generally extinguished. Convulsions occur in some cases, not in others; and certainly in some instances, if not always, the patient is unconscious during their continuance. Diplopia, or other disorder of vision, has been noted in some cases. Death may occur suddenly, especially *directly after some exertion* on the part of the patient, from syncope.

The symptoms produced by aconite in the lower animals are similar to those caused by it in man, the prominent manifestations being great disturbance of the respiration, muscular weakness, vascular depression, and finally death, with or without convulsions. As we have seen the rabbit after the injection of one-sixth or one-quarter grain of Morson's pure aconitine, the animal commences to jump vertically in a very peculiar manner, and often to squeal piteously. The jumping soon grows less and less powerful, and finally is replaced by severe convulsions, during which the animal often lies prostrate on its side. In the dog, however, the muscles have remained without a quiver during all stages of the poisoning; in the horse Harley[3] has noticed convulsions. The convulsions are an inconstant symptom, dependent upon peculiarities of the individual or species, as well as upon the amount injected. Dilatation of the pupil frequently occurs, if it be not, indeed, a constant phenomenon. There is often severe vomiting. Death usually results from asphyxia, but if a large dose be given hypodermically, may occur in less than a minute, probably from sudden paralysis of the heart-muscle.

Nervous System.—The mental condition in aconite-poisoning shows that the drug has no influence upon those portions of the cerebrum which are connected with consciousness and intellectuality.

Owing to the apparent contradictory character of the evidence it is difficult thoroughly to elucidate the action of aconite upon the lower portions of the nervous system; the phenomena to be accounted for are sensory paralysis, loss of reflex activity, and, later in the poisoning, motor palsy.

Nerves.—The local anæsthesia which is produced by the application of aconite demonstrates that the drug has, when in sufficient concentration, a paralyzing influence upon the sensory nerves.

The persistence of voluntary movement after abolition of reflex actions, which was first noted by Boehm and Wartmann,[5] and afterwards by Liégeois and Hottot,[4] as well as by Mackenzie, proves that at a certain stage of the poisoning, while the motor pathway from the brain along the ante-

* Laborde and Duquesnel affirm that after very large dose of aconitine the animal dies of spasm of the glottis and diaphragm, because they have noticed, especially in the young animal, drawing in or constriction of the lower chest during life, and *sub-pleural ecchymoses* after death. These are, however, the marks of paralysis of the glottis from palsy of the recurrent laryngeal nerve.

rior columns and the efferent nerves is open, either the sensory nerves or the receptive centres of the cord are paralyzed.

The discovery of Liégeois and Hottot—namely, that in the frog poisoned simultaneously with aconite and strychnine there is a certain stage when no amount of irritation of the nerve will induce convulsion, whilst a slight direct irritation of the cord will cause violent strychnic spasms—would seem to prove that at least the earliest abolition of the reflex activity is due to paralysis of the afferent nerve-fibres. In accord with this, Mackenzie found that when a nerve is protected from the poison by tying its supplying artery, irritation of it causes reflex actions when the remainder of the frog's periphery is insensible; that there is a stage of poisoning in which irritation of the extreme peripheral nerves fails to induce reflex movements, although such movements are called out by irritation of the sensory nerve-trunk; and that in the last stages of the poisoning irritation of the trunk is powerless, while irritation of the posterior columns of the cord still produces wide-spread movements. This evidence in its totality appears to us to prove that aconite *paralyzes the sensory nerves, commencing at their peripheral endings*, and that the loss of reflex activity is due, at least in great part, to this peripheral paralysis.*

Liégeois and Hottot affirm, however, that in the aconitized frog loss of sensibility occurs at a time when the reflex activity is intact. If this experimental fact be correct, it would seem to be an inevitable conclusion that the primary anæsthesia has its seat above the mechanism involved in reflex acts, or, in other words, in the perceptive centres of the brain. This theory is strongly urged by the French investigators mentioned, who further affirm that tying the aorta close to its abdominal bifurcation, so as to prevent access of the blood—*i.e.*, of the poison—to the posterior nerves, does not affect the development of the anæsthesia; also, that closing the artery nearer its origin in such a way as to shut off the circulation to the cord and spinal nerves, but to allow the passage of the blood to the cerebrum, does not cause sensory paralysis to come on more slowly than is normal in poisoning by aconite. Further, according to Liégeois and Hottot, in the frog doubly poisoned by aconite and strychnine there is a period in which reflex tetanic convulsions occur, although there is marked aconitic anæsthesia.†

* Laborde and Duquesnel (*Des Aconits*, Paris, 1883, 103) believe that they have demonstrated that aconitine does not act upon the sensory nerves. Their chief experiments consisted in tying the vessels of a dog's leg in such a way that no blood could return to the body, and injecting the alkaloid into the limb, after cutting the nerve. Under these circumstances they found that galvanization of the centric end of the nerve continued to elicit response. At most such experiments prove nothing as to the action of the poison upon the *peripheral nerve-endings*. Moreover, it remains uncertain whether the aconitine really came in contact with the divided nerve, as all circulation in the limb must have been arrested.

† Later in the poisoning the extreme peripheral nerves become affected, so that irritation of the skin in the doubly poisoned frog will not provoke convulsions, even at a time when irritation of the trunk of a nerve produces general reflex motor disturbance. At last galvanization of the nerve-trunk itself fails to induce response.

If the facts just enumerated be, as affirmed, correct, the conclusion seems to be almost inevitable that aconite influences the higher perceptive centres or general sensibility before it affects the peripheral sensory nerves. S. Ringer and H. Murrell[5] deny, however, the accuracy of the delicate experiments of Liégeois and Hottot, so that at present writing the matter remains in doubt.*

In regard to the action of the drug upon the motor nerves the evidence is somewhat contradictory. According to Achscharumow, when a frog is poisoned after the abdominal aorta has been tied, reflex and voluntary activity is preserved in the hind legs long after it has been lost in the anterior portion of the body ; and, at the same time, while the brachial nerves, as tested by galvanic stimulation, have lost their power of transmitting impulses, the protected ischiatic nerves have preserved their functional ability. P. C. Plugge[6] confirms these statements, and also affirms that it is especially the peripheral ends of the motor nerves which are affected, since when in the frog's leg the lower portion had been protected from the poison, galvanization of the nerve-trunk a considerable distance above the point of protection caused response in the tributary muscles.

These allegations would seem to prove that aconitine paralyzes the peripheral motor nerves, but are directly contradicted by Boehm and Wartmann, by Liégeois and Hottot, by Mackenzie[7] and by A. Guillaud,[8] who affirm that the nerves and muscles in poisoned animals preserve almost entirely their normal excitability until death, and that shutting off access of the poison to the limb by tying does not affect the development of motor paralysis under the action of aconite.

The explanation of this conflict of testimony is not to be found, as has been suggested by C. Ewers,[9] in the use of different species of frogs, because Plugge employed various species ; nor is it in the employment of different commercial aconitines, because Plugge experimented with all the varieties, and found them to vary in power, but not in quality of action. Those observers who have found least influence upon the motor nerves acknowledge some *slight* effect, and that when aconitine is brought in contact with an exposed nerve it rapidly destroys its functional activity ; also that after death in the aconitized frog the motor nerves lose their irritability more rapidly than normal (Liégeois and Hottot, Guillaud, S. Ringer and H. Murrell, Laborde and Duquesnel[10]).

From the evidence which has been thus epitomized it seems to us that the most probable conclusion is that aconite exerts a *feeble depressing influence upon the motor nerves.*

Spinal Cord.—Our knowledge of the action of aconite and its alka-

* Curiously enough, Ringer and Murrell, while doubting the experiments of Liégeois and Hottot, accept the conclusions founded upon these asserted erroneous experiments, seemingly because they themselves have found that aconitine causes abolition of reflex action more rapidly in brainless than in normal frogs. It is evident that even if this were invariably the case it would in no way prove the conclusions of Liégeois and Hottot. Further, the experiments on brainless frogs were only three in number, and it is probable that the rapid reflex palsy was simply the result of batrachian idiosyncrasies.

loids upon the spinal cord is not complete ; Boehm and Wartmann, Guillaud, Mackenzie, and Cash and Dunstan believe that after minute doses of aconitine there is primarily excitement or stimulation of the motor centres of the cord ; Mackenzie affirms that the convulsions which are so severe in the frog after small quantities of aconite are chiefly of spinal origin, though he believes that the peripheral motor apparatus shares the motor stimulation. If the primary stimulation of the cord really occurs in mammals, it must be completely masked ; at least we found in a series of experiments that when the spinal cord was cut in the mammal it was not possible to produce aconitic convulsions in those portions of the body separated from cerebral influence, and no evidences of spinal excitement are ever seen in human poisoning. The conclusion of Boehm and Wartmann, that in the later stages of the poisoning there is depression of the motor side of the spinal cord, is probably correct, but so far as we know has never been actually proved. The preservation of voluntary movements in the poisoned frog after the abolition of sensation and of the reflexes shows that the motor paths from the brain to the cord through the muscle are preserved at the time when the afferent apparatus is completely paralyzed, and that the action of aconite on the motor spinal cord is entirely subservient to its influence on the peripheral nerves.

Muscles.—The early evidence in regard to the action of aconite upon the muscles was entirely contradictory, Wieland, Bucheim, and Eisenmenger affirming that the muscle-curve is much affected by the drug, Murray and Boehm and Wartmann that it remains unaffected. The researches of Cash and Dunstan seem, however, to prove that aconitine does not increase the irritability of the muscle-fibre, nor when given in moderate doses affect its capacity for work, though in some way it predisposes the muscle to asynchronism in the contraction of its bundles of fibres.

Respiration.—Cash and Dunstan having noticed primary increase of the rate of the respiration by aconitine, believe that the alkaloid acts primarily as a centric respiratory stimulant ; but until it has been definitely proved that the amount of air forced in and out of the lungs is increased by aconitine, it must remain doubtful whether it ever has any true stimulant effect. When the poisoning is advanced the respirations in the mammal are slow, with a prolonged expiration following immediately upon the inspiration. After the expiration there is a long pause, so that the whole breathing-cycle resembles very much that occurring after section of the vagi. The known influence of aconite upon the peripheral afferent nerves in general suggests that the poison disturbs respiration by paralyzing the peripheral afferent fibres of the vagi, but Mackenzie states that in the aconitized animal section of the vagi produces no effect on the respiration ; and Boehm and Wartmann affirm that aconite produces its usual effect after division of the vagi. It is plain that even if the aconite does paralyze the peripheral afferent vagi it must also act upon the respiratory centres, since arrest of respiration could not be caused by afferent palsy. As the arrest occurs

in the frog before the motor nerves are affected by the poison, Liégeois and Hottot believe that the disturbance is centric ; and we think there can be no doubt that *aconite is a direct depressant and paralyzant of the respiratory centres.*

Circulation.—The action of aconite upon the circulation is very decided. In man it causes first slowing and later rapidity with irregularity of the pulse, accompanied by a fall of the arterial pressure, which progressively increases to the end. In frogs the phenomena caused by aconitine are similar to those seen in man, and consist of at first a reduction and afterwards an increase in the rate of the heart's beat, with a loss of power in the circulation, and finally irregular systolic movements, with marked prolonged diastolic pauses ending in diastolic arrest (Achscharumow,[11] Boehm and Wartmann).

In the mammal the general influence of aconite upon the circulation seems the same as in man, except that both in rabbits and in dogs a brief rise of pressure is affirmed to precede the fall (Boehm and Wartmann, Laborde, Duquesnel). It is probable, however, that this rise of pressure is secondary, and not directly caused by the poison. Very early the blood-pressure begins to fall ; after a time the fall becomes pronounced, and the pulse, which has been at first slowed, grows rapid. Then what is known by some observers as the characteristic condition develops, consisting especially of great and rapid fluctuations of pressure, which may in the dog amount to fifty millimetres of mercury, and may for the moment even carry the pressure to a higher than the normal point. The pulse finally becomes extremely rapid and irregular ; the heart is in a condition of delirium, and soon stops in diastole.

During the advanced stages of the poisoning the rhythm of the mammalian heart is seriously affected, the contractions of both auricle and ventricle being very unequal, and the normal auricular and ventricular rhythm seriously impaired (see S. A. Matthews,[12] also J. T. Cash and W. R. Dunstan). The intra-ventricular pressure also varies greatly, and the whole action of the heart is in such a state of confusion as most seriously to interfere with the coronary supply and the general mechanism of the circulation. After death the cardiac muscle fails to respond to galvanic irritation.*

The cardiac phenomena which have just been noted are most clearly seen after the use of pure aconitine (Cash and Dunstan), and under these circumstances it is affirmed that until the later stages of the poisoning are reached there is no distinct loss of force in the individual systole, the muscle itself not being affected.

In endeavoring to elucidate the cause of the cardiac phenomena of aconite-poisoning it is evident in the first place that aconite affects the heart directly. Achscharumow affirms that aconitine acts upon the frog's

* According to S. A. Matthews, during the period of delirium of the ventricle the auricle can generally be restored to regular contraction by cutting one of the big veins and allowing it to free itself of the contents.

heart removed from the body as it does upon the heart of the normal batrachian. Liégeois and Hottot have produced the ordinary cardiac phenomena of aconite-poisoning by placing the alkaloid upon the heart.

The first question that offers itself is as to the cause of the primary slow pulse.

Boehm and Wartmann affirm that the development of the slow pulse is not prevented by the previous section of the vagi or by atropinization. Achscharumow, however, states that section of the vagi performed during the early stage of aconite-poisoning is followed by a pronounced immediate rise both in the number of the cardiac pulsations and in the arterial pressure. Lewin [13] affirms the correctness of this, but states that the rise is of very brief duration, and is soon followed by the usual reduction. *S. A. Matthews states, however, that after section of the vagi aconite reduces the heart's rate to a slight extent only, and that even this reduction is entirely prevented by the administration of atropine. Cash and Dunstan affirm that section of the vagi in the period of slow pulse from aconite is followed by an immediate increase of the rapidity of the beat.

The concordance of recent investigators warrants the conclusion that aconite primarily slows the heart by stimulating inhibition ; the stimulation being chiefly centric, but, if the experiments of Matthews be correct, being also in a measure peripheral.*

The rapid pulse of the advanced stages of aconite-poisoning is attributed by S. A. Matthews chiefly to the ever-increasing irritability of the cardiac muscle under the action of aconitine, and to us seems to be in part due to the action of the alkaloids upon the heart-muscle, and to be also in part the outcome of depression of the peripheral vagi.

The evidence given by different experimenters in regard to the condition of the peripheral vagi in aconite-poisoning is somewhat contradictory. Boehm and Wartmann, and Plugge, affirm the existence of vagal paralysis. S. A. Matthews says that "the peripheral inhibitory mechanism is not paralyzed by the aconitine during the irregular stage, as is generally stated ;" but we have no doubt as to the accuracy of the assertion of Cash and Dunstan, that, although when the dose of aconitine has been so large as to be rapidly lethal the vagal terminations may not be completely paralyzed up to death, when small lethal doses have been used, complete peripheral vagal paralysis may develop, or a condition appear, also noted by Boehm, in which the vagi may respond one minute to stimulation and refuse to respond the next.

Our knowledge of the action of aconitine upon the vaso-motor system is not complete. The paralysis of the afferent nerves in advanced aconite-poisoning, by shutting off from the vaso-motor centre the impulses which normally reach it from without, must certainly affect the general tone of the vessels, a reasoning which finds strong confirmation in the fact asserted

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* The activity of aconite depends chiefly upon the aconitine. According to Cash and Dunstan, *benzaconine* chiefly depresses the motor mechanism within the heart, also depresses the vaso-motor centre, causes slow pulse by vagal stimulation, and is the antagonist of digitalin. *Aconine* is so feeble as to be disregarded in considering the effect of aconite. According to Cash and Dunstan, it has a curare-like action on the motor nerves, stimulates the roots of the vagi, strengthens the ventricular systole, and does not affect the vaso-motor centre.

by Boehm and Wartmann, that there is a stage in aconite-poisoning in which galvanization of a sensitive nerve does not produce rise of the arterial pressure, which, however, is developed at once when the vaso-motor centres in the medulla are stimulated.

S. A. Matthews and Cash and Dunstan affirm that the first action of the drug upon the vaso-motor centre is as a stimulant, but we have not been able to find in their papers any sufficient proof of this, and do not believe that the conclusion is probable. It is likely that in the advanced stages of the poisoning the vaso-motor centre is depressed or paralyzed, though this has not been positively proved. The best evidence is that furnished by Cash and Dunstan,—namely, that there is a period in which mechanical asphyxia ceases to elevate the pressure.

That the efferent vaso-motor apparatus is not paralyzed is shown by the facts that in advanced poisoning galvanization of the sympathetics in the neck causes contraction of the vessels (Nunneley [14]), and that the splanchnics retain almost to the last their functional activity.

Temperature.—In the very beginning of aconite-poisoning the bodily temperature may rise slightly, but in severe poisoning a very pronounced fall occurs. The reduction of the bodily heat is probably caused by an increase of heat-dissipation. If vaso-motor paralysis occurs in aconite-poisoning it will account for this loss of heat. Further, it is entirely possible that aconite, without producing vaso-motor paralysis, may, by destroying the conducting power of the afferent nerves, put an end to the automatic relation between heat-production and heat-dissipation. In accord with this is the observation of Brunton and Cash,[15] that in animals exposed to a high temperature, aconite, far from depressing the temperature, favors its increase, while when the animal is exposed to cold, aconite accelerates the fall of the bodily heat remarkably (confirmed by Cash and Dunstan).

SUMMARY.—Locally, aconite is slightly irritant at first and subsequently paralyzant especially to the sensory nerves. It yields its active principle rapidly to absorption. Aconite has little direct action upon the cerebrum, unless it be upon the perceptive centres of general sensibility, concerning which there is still dispute. It is asserted by some authorities that the small dose stimulates respiration, but this has not been proved. In toxic dose it acts as a powerful depressant to the respiratory centres, and usually kills by centric paralytic arrest of respiration. It also paralyzes the peripheral fibres of the vagus in the lungs, and thereby notably affects respiratory rhythm. Its action upon the spinal cord remains uncertain, some authorities believing that it primarily stimulates the motor side of the cord, and very late in the poisoning causes centric motor depression. Its dominant influence, so far as the nervous system is concerned, is, however, upon the sensory nerves, affecting primarily their peripheral filaments and involving later their trunks. It has also some, but a much less powerful, depressive action upon the motor nerves. According to some authorities, the stage of nerve-paralysis is preceded by one of nerve-stimulation, but this is extremely doubtful.

Aconite reduces very markedly the rate of the pulse and the arterial pressure, the primary stage of slow pulse being followed by one of rapid irregular pulse, with very fluctuating but still low pressure. The chief cause of the slow pulse is stimulation of the vagal nerve (aconitine, benzaconine), which is followed, when the rapid pulse comes on, by depression of the peripheral vagi. The rapid pulse is in part due to the withdrawal of inhibition, and probably also in part to a direct action of aconitine upon the muscle-irritability. Aconitine appears primarily not to affect the muscular strength of the heart, but on account of the depressing influence of the benzaconine upon the muscle the cardiac force is weakened by aconite from the beginning.

The action of the drug upon the vaso-motor system is not established; several recent observers affirm that the first action of the drug upon the vaso-motor centre is stimulation, which seems to us to be unproved and improbable; in the advanced stages of the poisoning the vaso-motor centre is probably depressed or paralyzed, but even concerning this our knowledge is uncertain. The efferent vaso-motor nerves are not affected.

The bodily temperature is reduced by aconite by an increase of heat-dissipation, and perhaps also by an action on the thermo-genetic nervous system. On the glandular system of the body, except that of the skin, aconite has little or no influence.

THERAPEUTICS.—The general indication for the use of aconite is to lower arterial action, but the selection of this drug among other cardiac depressants for this purpose should be governed by certain definite principles, depending upon the known peculiarities of its action. When the high arterial pressure is chiefly cardiac in origin, it is the best drug of its class, having in therapeutic dose little or no influence upon the system other than upon the heart, and producing no disturbance of gastric or intestinal digestion. Further, aconite has a certain permanence of action not equal to that of digitalis but greater than that of the other cardiac depressants. No cases or reports of cases of cumulative effects parallel to those caused by digitalis have come under our notice, but when small doses are given continuously there is a progressive increase of effect. In cases of *cardiac hypertrophy*, or when there is in valvular disease excessive compensation, aconite is the best remedy that we have. Given in doses of the tincture, from two to five minims three times a day, it acts steadily and persistently. When the administration is free, the effect should always be watched carefully and the dose lessened *pro re nata*.

On the other hand, when a sudden, very powerful influence to meet an emergency is desired, and especially when it is necessary if possible to produce wide-spread vaso-motor weakness and consequent relaxation of the blood-vessels, aconite should not be employed. The overdose is more apt to produce serious results than is the overdose of veratrum viride, and the effect of it upon the blood-vessels is far less than is that of veratrum viride.

In the forming stage of sthenic *pneumonia* aconite cannot be substituted with any justification for veratrum viride. On the other hand, in *irritative fevers*, as the *ephemera* of childhood from gastro-intestinal

irritation or other cause, aconite in moderate dose often acts most happily. Especially is it useful in combination with other drugs which have a tendency to increase the secretion from the skin, when it is desired to produce free sweating. If only a moderate but continuous skin effect is desired, aconite may be given with neutral mixture; to it may be added, if circumstances favor, antipyrin. When it is desired, as in acute *muscular rheumatism* or in a forming *grippe*, to produce very free sweating, a combination of aconite, pilocarpine, and antipyrin is very effective. In a *urethral fever* due to the passage of the catheter or bougie, aconite often acts most happily.

A second indication which aconite might be used to fulfil is to *allay spasm*. As, however, its influence upon the motor centres and nerves is much less than upon the sensitive centres and nerves and upon the heart, the indication is better met by other remedies.

A third indication, which it would seem from its known physiological action that aconite should meet, is to *relieve over-excitation of the sensitive nerves*. Although aconite was formerly very much used for the relief of pains which were called *neuralgic*, and is sometimes useful when an acute *neuritis* has followed exposure to cold, and is of a rheumatic type, it is rarely of real service even as a local remedy, and is of no value whatsoever in such diseases as *migraine* when the pain is of centric origin.

Given in full doses in the reflex *vomiting* of *pregnancy*, aconite is often advantageous, acting probably by benumbing the sensory reflex centres, or possibly the afferent peripheral gastric nerves. We have noticed that relief lasts only so long as decided constitutional effects from the drug are apparent.

Toxicology.—Aconite is an exceedingly powerful poison; one-twelfth of a grain of the crystallized aconitine is, according to Duquesnel, sufficient to kill a rabbit in a short time. Five grains of an extract and eighty minims of a tincture are said to have caused death (Reichert[16]). The symptoms usually come on in a very few minutes. In the shortest case we have met with, death occurred in thirty minutes. The average time of death (Reichert) is three and a third hours, the longest recorded case being five and a half hours.

The *aconitines* of commerce vary inordinately in strength, so that while one-sixteenth of a grain (prepared by Petit,* of Paris) caused the death of Carl Meyer

* In the researches of Anrep, Duquesnel's crystallized aconitine was nearly twice as strong as a German alkaloid used by him, which in turn was much stronger than an English article. Plugge found Petit's aconitine eight times as strong as that of E. Merck. Langgaard found an alkaloid prepared from *A. japonicum* exceedingly powerful. The best discussions of the relative strength of these alkaloids that we know of may be found in *Schmidt's Jahrb.*, ccii. 124, and in *Des Aconits*, by J. V. Laborde and H. Duquesnel, Paris, 1883. Lhôte and Vibert (*Annal. d'Hyg. Publ.*, 1892, xxviii.) assert that the crystallized aconitine of Duquesnel is an essentially different poison from the amorphous aconitine of commerce or from the aconitine sulphate of Merck. The latter in the isolated frog's heart they found to produce gradual progressive enfeeblement, whilst the Duquesnel aconitine caused primarily great increase in the size of the cardiac pulsation, with periods of ataxia, followed by depression.

in five hours, and a quarter of a milligramme is said to have produced violent poisoning, several grains of the impure article so largely sold have been recovered from. The symptoms were in general those of aconite-poisoning, but excessively violent pains and convulsions have been very marked features of some of the cases. (For discussion of aconitine-poisoning, see Thomas Stevenson,[17] M. Jules Bassot,[18] also six cases, Lhôte and Vibert.[19])

The only diagnostic symptom of aconite-poisoning is the peculiar tingling, which is probably always present, though in suicidal cases the patient may refuse to reveal it, or in advanced poisoning unconsciousness may prevent its being told. The presence in any case known to be one of poisoning of absolute prostration with almost complete failure of the pulse, great muscular relaxation, and other symptoms of collapse, without vomiting, purging, or any disorder of the pupil or other toxic manifestations, is sufficient for a working diagnosis.

The first indication for treatment in aconite-poisoning is evacuation of the stomach ; as emetics usually fail, on account of the local gastric anæsthesia, the stomach-pump may often be used, but the danger of causing fatal collapse in extreme cases must not be overlooked. Tannic acid may be administered as an imperfect antidote. Hot concentrated alcoholic stimulants should be freely given ; strychnine, atropine, and digitalis * should be used hypodermically with great boldness, tempered with caution. Ammonia may be injected into the veins, if it be found practicable. The patient must be kept upon the back, with the feet a little higher than the head, and external heat be used freely to maintain temperature. Laborde and Duquesnel affirm that in the lower animals death after a usually fatal dose of aconitine can be prevented by artificial respiration ; and in a case of human poisoning, if the heart's action were at all sustained, and the respiration failing, Sylvester's method or forced artificial respiration might be resorted to.

ADMINISTRATION.—Aconite is never used in substance. Dose of tincture of aconite (TINCTURA ACONITI—thirty-five per cent., U. S.), one to five minims (0.06–0.30 C.c.), repeated every one to three hours

* The original discovery of J. Milner Fothergill (*Digitalis*, London, 1871, 6), that digitalis is the cardiac antagonist of aconite, has been abundantly confirmed. The careful work of Matthews and of Cash and Dunstan has demonstrated that it is benzaconine which is especially antagonized by the digitalin, atropine being the cardiac antagonist of aconitine. Clinical experience, although still limited in extent, strongly corroborates the experimental evidence of the value of digitalis. Successful cases may be found in *Brit. Med. Journ.*, Dec. 11, 1872 (f℥i Fleming's tincture, Tinct. digitalis ♏x hypodermically) ; *Bost. Med. and Surg. Journ.*, Oct. 1879, 544 (f℥iii Tinct. aconit. rad., Tinct. digitalis ♏lx hypodermically) ; *Indian Med. Gaz.*, xvii. 323 (Aconitum ferox root forty-eight grains, Tinct. digitalis ♏xxv hypodermically and f℥i by mouth) ; *Phila. Med. Times*, xiii. 328 (a decoction of aconite, amount unknown, Tinct. digitalis in drachm and half-drachm doses, by mouth). In a successful case treated by Elliot (*Lancet*, 1878, ii. 917) amyl nitrite freely inhaled seemed to do great good : a fluidounce of a concentrated aconite liniment was thought to have been taken. Ammonia injections were unsuccessful in a case reported in the *Australian Med. Journ.*, 1879, i. 283. G. H. Tuttle (*Boston Med. and Surg. Journ.*, 1891, cxxv.) has reported recovery after seven and a half drachms of the tincture, under the free hypodermic use of brandy and digitalis, the same remedies with tincture of nux vomica being given internally, and auxiliary measures used.

pro re nata, its effects being always watched. *Fleming's tincture* is a stronger preparation (ten and a half ounces to a pint). Dose of extract (EXTRACTUM ACONITI, U. S.), one-quarter to three-quarters of a grain (0.016–0.049 Gm.); of fluid extract (EXTRACTUM ACONITI FLUIDUM, U. S.), one to two minims (0.06–0.12 C.c.). The tincture or the fluid extract of aconite is very frequently added to stimulating and anodyne liniments.

Owing to its varying purity and composition and its extraordinary activity, aconitine should not be used in practical medicine. According to E. Tison, the dose of the nitrate is one-tenth of a milligramme.

ACIDUM HYDROCYANICUM—HYDROCYANIC ACID.

Pure hydrocyanic acid is a colorless, transparent, volatile, inflammable liquid, giving rise to giddiness and headache when smelled, and having, it is said, a burning, bitter taste. So poisonous is it that when inhaled it causes death, and it must be handled with the greatest caution: smelling and tasting it are excessively dangerous proceedings. It is, indeed, an imperative rule that no one should experiment with anhydrous prussic acid alone, or under any circumstances in summer, or in a warm room, or in an apartment whose open windows and doors do not admit of a free draught of air. The chemist Scheele, the discoverer of prussic acid, is believed to have been killed by the inhalation of the fumes of this material, whose poisonous properties were first pointed out by the Berlin apothecary Schrader in 1803. The anhydrous acid is soluble in water and in alcohol, but is never kept in the shops, and is not official.

Hydrocyanic acid of common medical parlance is the official *Dilute Hydrocyanic Acid* (ACIDUM HYDROCYANICUM DILUTUM, U. S.), a colorless, watery solution, containing two per cent. of the anhydrous acid. Its odor and taste are the familiar ones of peach-kernels and bitter almonds; its reaction is faintly acid. As it has a great tendency to undergo spontaneous decomposition, especially under the influence of light, it should be kept in well-stopped, dark-colored bottles.

PHYSIOLOGICAL ACTION.—*Local Action.—Absorption and Elimination.*—Hydrocyanic acid appears to be free from irritant properties, but is a universal depressant poison, capable, when in sufficient amount, of paralyzing all higher tissues, and having, when applied locally, an especially powerful influence upon sensory nerve-endings. It is absorbed with almost instantaneous rapidity through all mucous membranes. Concerning its fate in the body we have no knowledge except that it is either destroyed or eliminated with the greatest rapidity, so that its action is extremely fugacious.

General Action.—The symptoms produced by prussic acid in man are so rapid in development and course that usually the patient is dead or convalescent before seen by the physician. The ordinary therapeutic dose produces no distinct manifestations; after the toxic dose the symptoms come on suddenly. In a moment or two the individual falls to the

ground insensible and convulsed, the respirations arrested or occurring at long intervals, the eyes salient, the pupil dilated, the mouth covered with bloody froth. If the dose be sufficiently large, death may occur in three or four minutes; if less has been taken, deep insensibility, tetanic or clonic convulsions, dilated pupils, a bloated countenance, cyanosed surface, set jaws, and irregular respiration constitute the chief symptoms. The breathing is mostly convulsive, with deep, forcible expirations, but in some cases it has been stertorous. Death results from asphyxia. After small toxic but not lethal doses of prussic acid, giddiness, lightness of the head, nausea, a quick pulse, and muscular weakness are the chief symptoms.

After a full dose of the strong anhydrous prussic acid, the lower animal gasps once or twice, and then instantly falls in a tetanic or clonic convulsion, or else drops motionless and powerless upon its side, heart and lungs ceasing almost at once. After a smaller toxic dose the signs of asphyxia at once manifest themselves, and grow more and more intense, until they end in total arrest of respiration. The heart beats irregularly, often at first slowly and strongly, with intervals of suspension of movement, but always becoming weaker and more rapid in its action, until, after the breathing has ceased, its efforts gradually die away. Ordinarily, three distinct stages are apparent: a first, very brief one, of difficult respiration, slow cardiac action, and disturbed cerebration; a second, convulsive stage, with dilated pupils, violent convulsions, unconsciousness, loud cries, vomiting, often spasmodic urination and defecation, erections, etc.; and a third period, of asphyxia, collapse, and paralysis, sometimes interrupted by partial or even general spasms.

The slow form of the poisoning follows the exhibition of the poison in an amount just sufficient to kill. After the ingestion of such a dose, no phenomena are offered for some seconds; then the breathing becomes labored and the pulse slow and full. The animal perhaps cries out, and muscular tremblings rapidly grow into clonic and tonic convulsions, which continue at intervals until the third stage—that of collapse—is developed. When the third stage is developed, the anæsthesia is marked, affecting first the hind legs, but finally spreading to all parts of the body, and even being complete in the widely dilated pupil. Death finally results from failure of respiration. Recovery may occur even after the conjunctiva has lost its sensibility; the return to life by a subsidence of the symptoms is usually rapid, so that generally in from one-half to three-quarters of an hour the animal will be eating as though nothing had happened. Coullon, however, noted persistence of paralysis, in some cases, for days.

Blood.—Prussic acid has a very decided influence upon the blood, which may after death be found uniformly of a bright arterial or a deep venous hue.

F. B. Vietz,[1] E. L. Schubarth,[2] J. F. Sobernheim,[3] Coze,[4] Claude Bernard, and others all affirm that when an animal is killed abruptly with hydrocyanic acid the blood in the veins and right heart is of a bright arterial hue. In 1844, however, J. R. Bischoff[5] affirmed that in man and in mammals killed with prussic acid nothing could be found but dark venous blood in either artery or vein, an observation which has been since confirmed. The explanation of these discrepancies was first given by W. Preyer,[6] and subsequently confirmed by Carl Gaethgens;[7] directly after the administration of the poison, in the mammal the venous blood becomes almost immediately of a bright arterial hue, which, however, rapidly darkens until all the blood of the body is venous. If the mammal dies suddenly from car-

diac paralysis during the first stage of the poisoning, this excessive arterialization may be found after death, and in cold-blooded animals the bright color persists for many hours (Preyer). If, however, life is more prolonged, the blood grows dark.

According to Gaethgens, the scarlet venous blood of the first stage of the poisoning shows clearly the absorption bands of oxyhæmoglobin under the spectroscope, whilst Preyer has demonstrated that the dark blood of the advanced stages of the poisoning gives only the lines of reduced hæmoglobin.

There has been much discussion as to the cause of these changes in the blood. Hoppe-Seyler believes that the scarlet venous blood of the first stage of the poisoning is due to the suspension of the power of the red blood-corpuscles to yield up their oxygen. Carl Gaethgens determined that during this first stage there is a limited elimination of both carbonic acid and oxygen from the lungs. At the same time the percentage of carbonic acid in the expired air is less, and that of oxygen is greater, than in the normal air, showing that in some way the conversion of oxygen into carbonic acid is interfered with. It is clear that during the first stage of prussic acid poisoning oxidation is arrested. That this arrest of oxidation is due, as believed by Hoppe-Seyler, to the action of the poison upon the red blood-corpuscles seems to us improbable, since it has been proved by Gaethgens that when the experiments are prolonged there comes a time when more than the normal amount of carbonic acid is eliminated,—a fact in accord with the excessive carbonization of the blood which occurs in the later stages of protracted hydrocyanic acid poisoning. In the advanced stages of the poisoning the red corpuscles must, therefore, be functionally very active.

As first discovered by Hoppe-Seyler,[8] and afterwards confirmed by Preyer, when hydrocyanic acid is added to blood outside of the body there is produced a new substance giving rise to new spectroscopic lines and without ozonizing power, the so-called *cyanohæmoglobin*. It has been determined by Schönbein that hydrocyanic acid destroys the ozonizing power of living vegetables, such as roots, fungi, etc., and also of blood to which it is added outside of the body. In regard to the latter fact some confirmation has been afforded by Harley, who found that the dark blood taken forty-eight hours after death from the subject of prussic acid poisoning, shaken with air, and allowed to stand, yielded gas containing about twenty per cent. of oxygen, eighty of nitrogen, and no carbonic acid. It is proved that the dark blood of prussic acid poisoning, shaken with the air, assumes the red arterial hue, and Lecorché and Meuriot[9] have shown that artificial respiration will produce the same result in the poisoned animal. On the other hand, it has been spectroscopically proved that there is no cyanohæmoglobin in the blood of the poisoned animal, the hæmoglobin existing in the blood either as hæmoglobin or oxyhæmoglobin (Preyer, Laschkewitsch,[10] Hiller and Wagner[11]).

The facts just epitomized would seem at first sight very strong evidence of the correctness of the theory of Hoppe-Seyler, that hydrocyanic acid in the first stage of the poisoning paralyzes the ozonizing power of the red blood-corpuscles ; but it seems very difficult to see how a substance should in the first stage of poisoning paralyze the ozonizing power of the red blood-corpuscles and in the next stimulate such power so that the blood should become dark and loaded with carbonic acid. Further, it has been shown by Preyer that the excessive oxygenation and the subsequent excessive carbonization of the blood are not peculiar to hydrocyanic acid poisoning, but are equally present after the exhibition of sulphuretted hydrogen, and even after mechanical closure of the mouth and nose. It is possible that a heightened arterial pressure producing an increased rapidity of circulation may cause the blood to pass too quickly

through the capillaries to allow time for the usual changes ; but this has not been proved, and at present it must be acknowledged that we are ignorant as to the immediate cause of the blood-changes in these cases.

Alterations in the form of the corpuscles of the blood have been suggested as the cause of the changes of the color, Ernst Geinitz having found that both in the frog and in the mammal prussic acid distorts the blood-corpuscles. On the other hand, in the observations of Preyer, although such alteration of the blood-corpuscles could be produced in mammalian blood outside of the body, yet in blood drawn immediately after death from prussic acid the corpuscles offered their usual character ; a fact confirmed by Hünefeld.[12] *

Whatever may be the cause of the changes in the blood, the experiments of Lewisson[13] would appear to prove that the action of the poison on the nervous system is a direct one, and not due to these changes in the vital fluid, for the observer mentioned found that prussic acid acted upon the bloodless "salt frog" as upon the normal batrachian.

Action on the Heart.—The action of hydrocyanic acid upon the *heart* varies according to the dose. In sufficient amount and concentration it produces instantaneous diastolic arrest, which is either permanent or reoccurs after a few slow feeble beats (Preyer, and Lecorché and Meuriot). As early as 1826 Krimer found that prussic acid placed directly upon the heart of the frog produces arrest of its beat and loss of its muscular irritability. Preyer has confirmed this, and it would seem to be proved that the cardiac arrest spoken of above is due to a direct action upon the heart-muscle or its contained ganglia, yet that after cardiac death from prussic acid the heart responds to galvanism.

The cardiac results of the exhibition of small non-toxic doses are, according to Preyer, simply slowing of the heart's action.

Preyer and Laschkewitsch agree as to the action of large, but not enormous, doses. At first there is a sudden prolonged diastolic arrest of the heart, followed by an augmentation in the rapidity of the cardiac action, and after this a diminution of the rate,—to the normal number in cases of recovery, to cardiac stand-still in cases of death. Both Preyer † and Laschkewitsch found that after section of the vagi the primary diastolic arrest of the heart did not occur. Jos. Lazarski[14] has also

* According to E. Ray Lankester (*Pflüger's Archiv*, 1869, 492), when blood is shaken with cyanogen gas, and allowed to stand for two or three hours, the spectrum-changes are exactly the same as after similar treatment of blood with CO. The compound of cyanogen and hæmatin (Cy,Hb) offers not only the identical spectrum of CO,Hb, but also, like the latter, is unaffected by reducing agents. After the blood stands awhile, according to Lankester, the spectrum of hydrocyanic acid (H,CN) becomes visible in it, and the Cy,Hb undergoes conversion into the cyanohæmoglobin (Cy,Hb) of Hoppe-Seyler.

Any one desirous of investigating this subject more deeply than can be done in a work like the present should consult especially the papers by Hoppe-Seyler (*Virchow's Archiv*, xxxviii., and scattered through the *Med.-chem. Untersuchungen*), by Harley (*Lond. Phil. Trans.*, 1865, 706), and by Preyer (*Pflüger's Archiv*, 1868, 395).

† Preyer (*loc. cit.*, 93) has also noted the same absence in curarized animals poisoned by hydrocyanic acid.

found that the slowing of the pulse by moderate doses of hydrocyanic acid is prevented by previous section of the vagi. It would seem, therefore, proved that small doses of prussic acid *stimulate the cardiac inhibitory nervous centres.* Boehm and Knie[15] noted that large doses of the acid caused slowing of the pulse whether the vagi were cut or not, and in this have been confirmed by Lazarski. This slowing would seem to be due to a direct action upon the muscle or the intra-cardiac ganglia, as Lazarski found that the cardiac accelerator nerves are not paralyzed.

Moderate doses of prussic acid seem to produce a primary very brief but great rise in the arterial pressure, followed by a fall to or below the normal. This primary rise has been noticed by Boehm and Knie, by Wahl,[16] by Rossbach and Papitzky,[17] and by Lazarski. It does not seem to be altogether the result of the asphyxia produced by the acid, as it is recorded by Boehm and Knie as occurring when artificial respiration was used, and Lazarski has confirmed this. All observers agree that it is followed, if the dose of the poison has been large enough, by a profound sinking of the arterial pressure. Lazarski found that galvanization of a sensitive nerve has no effect at this time upon the blood-pressure : so that we must consider that hydrocyanic acid *primarily stimulates very briefly the vaso-motor system directly or indirectly, and afterwards paralyzes it.*

Action on Respiration.—According to Preyer, during all three stages of hydrocyanic acid poisoning the respirations are lessened in frequency, and during the latter moments of life the efforts at breathing are very distant, and finally cease before the arrest of cardiac movements.

Preyer found that, after division of the vagi, normally lethal doses did not kill, and that when death was brought about by the exhibition of larger doses it was by cardiac arrest. From this he deduces the conclusion that the prime respiratory action of the poison is upon the peripheral ends of the vagi. Preyer's experiments have been partially confirmed by Lecorché and Meuriot; but Boehm and Knie have in a series of experiments found that section of the vagus has no influence upon the respiratory action of the poison, and in this have been confirmed by Jos. Lazarski. Even if investigations had proved the correctness of Preyer's experiments, his conclusion could not be considered established, because we know so imperfectly the normal relations of the pneumogastrics to respiration. Moreover, Joseph Jones[18] found that while to kill an alligator by the administration of prussic acid required a considerable length of time, its application to the medulla produced within one minute a most powerful expiration, ending in permanent contraction of the muscles of respiration and collapse of the lung.

We must, it seems to us, at present consider that the respiratory phenomena of prussic acid poisoning are due to an influence exerted directly upon the respiratory centre.

Action on Muscles and Nerves and Nerve-Centres.—Kölliker[19] has found that in frogs dead of prussic acid poisoning both the nerve-trunks and the muscles are unexcitable, or that the muscles respond very feebly to direct stimulation.

He also showed that protecting the nerve-trunks by tying their supplying artery prevented any loss of function in them when the animal was poisoned, and

that the conclusion of Stannius,[20] that prussic acid applied locally to the nerves has no effect upon them, was due to his having used on the nerve employed for comparison a fluid almost as deadly as the prussic acid.

The experiments of Kölliker are in agreement with those of Stannius, that the muscle dies very much more quickly in the solution of the acid than does the nerve, losing its excitability in from seven to eight minutes.

This rapid destruction of muscular irritability by the local application of prussic acid was, we believe, first noted by Coullon in 1819. Yet it is most probable that when given internally prussic acid acts almost as rapidly upon the nerve-trunks as upon the muscles, since Kölliker noted that in some cases galvanization of the nerve was incapable of causing contractions in the tributary muscles, although the latter responded feebly to direct stimulation. This fact has been experimentally corroborated by Funke.[21]

Upon the peripheral sensitive nerves prussic acid, if in sufficient concentration, acts as a paralyzant.

Kölliker found that if the leg of a strychnized frog, whose heart had been cut out to prevent absorption, was put in a four per cent. solution of prussic acid, in a very short time irritation of the immersed skin ceased to produce convulsions.

From the slowness with which, in Kölliker's experiments, the nerve-trunks were affected in frogs poisoned by hydrocyanic acid, it seems probable that he is correct in his conclusion that in these batrachians the poison first paralyzes the brain, then the reflex centres of the spinal cord, and afterwards the motor nerves. But we have not met with any experimental evidence in regard to the order in which prussic acid affects the nervous system.

According to Kiedrowski* (quoted by Preyer), in frogs it first paralyzes the gray, then the white substance of the brain, and the early disappearance of reflex movements is not due to spinal palsy, but to destruction of the functional power of the peripheral afferent nerves. Preyer also states that the conclusions of Kiedrowski rested upon the following experimentally proved fact, which, if accurate, seemingly renders them logically inevitable. When a frog is poisoned with prussic acid, and afterwards with strychnine in properly proportioned doses, there is a stage at which slight irritation of the afferent nerve-roots causes violent general tetanic spasms, although the most intense peripheral irritation fails to elicit response.

It is a question of interest to decide as to the cause of the convulsions in poisoning by hydrocyanic acid. We have found that they do not occur after section of the cord in parts below the point of section, and that they are therefore cerebral in origin. It is probable that the convulsions are secondary, asphyxial, or due to disturbance of circulation.

* We have, unfortunately, been unable to obtain access to the original paper of E de Kiedrowski. Even Preyer appears to know it only in abstract. According to him, it was published in 1858, at Breslau, as a dissertation, under the following title: *De quibusdam experimentis quibus quantam vim habeat acidum hydrocyanicum in nervorum systema cerebro-spinale atque in musculos systematis vertebralis probatur.*

Laschkewitsch, who opened the thorax of a rabbit so as to expose the heart, maintained artificial respiration, and administered prussic acid; directly after arrest of the heart had commenced the convulsions came on; also in the earlier observation of Coze,[22] the convulsions did not occur until directly after the arrest of the circulation. In frogs poisoned with hydrocyanic acid, convulsions do not take place. Preyer states that after section of the vagi convulsions do not generally happen in mammals, but if artificial respiration be performed they come on.

SUMMARY.—When in sufficient concentration hydrocyanic acid is a powerful depressant poison to all the higher tissues. It is absorbed immediately, and acts at once, but so fugaciously that its influence is over in a few minutes. In poisoning by it death usually occurs through centric paralysis of the respiration, but the depression of the heart's action is pronounced, and diastolic cardiac arrest sometimes takes place simultaneously with or even before cessation of breathing. It first stimulates, then paralyzes the vagi; it first stimulates, afterwards paralyzes the vaso-motor system. Upon the nerve-centres it has a most pronounced depressing influence, and it is also a paralyzant to the nerve-trunks and to the muscles themselves. There is some reason for suspecting that after the small toxic dose of hydrocyanic acid the paralytic stage is preceded by a very brief stage of excitement, with centric increase of the respiratory activity, rise of the arterial pressure (caused by an influence upon the vaso-motor centres and perhaps upon the heart), and slowing of the pulse from stimulation of the cardiac inhibitory centres. Outside of the body hydrocyanic acid attacks the red blood-corpuscles, forming a new compound, cyanohæmoglobin; but the occurrence of this change during life in hydrocyanic acid poisoning is doubtful.

THERAPEUTICS.—Our knowledge of the physiological action of prussic acid does not lead to a belief in its wide applicability to the relief of disease, and we think that clinical experience has demonstrated that it is of little value except in meeting three indications: first, *to allay cough*; second, *to relieve irritation of the gastric nerves*; third, *to allay irritation of the peripheral sensitive nerves*.

Prussic acid has been used very largely to allay cough, either itself or in the form of potassium cyanide. Owing to the extreme fugaciousness of its action, it is, however, of very little real value for this purpose. It is not probable that the effect of any therapeutic dose of the acid lasts over twenty minutes, or of the cyanide over forty-five minutes.

There can be, on the other hand, no doubt as to the value of prussic acid in certain stomachic affections, especially nervous *vomiting* and *gastralgia*. When the pain is accompanied by decided dyspeptic symptoms, the remedy will sometimes succeed, but more often fails. Even in the most favorable cases it does not always afford relief; and as the relief when it does occur is immediate, or at least is very soon apparent, it is useless to persist long in the exhibition of the remedy. In these cases its action is probably local, as it certainly is when the acid is employed to relieve itching in *prurigo* and other cutaneous diseases. For

this purpose it is used as a wash (one-half to one fluidrachm in one fluid-ounce); but great care must be taken to avoid constitutional effects, especially when there is any abrasion of the skin. Very serious results are said to have been caused by its absorption when carelessly used in skin diseases.

Prussic acid has been commended as an arterial sedative; but unless given in dangerous doses it has no such action.

TOXICOLOGY.—The symptoms of prussic acid poisoning have already been mentioned: those of most value from a diagnostic point of view are the sudden occurrence of unconsciousness, the violent convulsions, the general paralysis, the peculiar character of the breathing, expiration being prolonged and forced, and the rapid results. The odor of prussic acid upon the breath is very often, but by no means always, present. When distinct, it is, of course, of great diagnostic value. Leaving out of sight the cyanides, the only poison with which prussic acid could well be clinically confounded is nitrobenzol. The distinction is often very difficult, large doses of the latter substance killing almost as quickly as prussic acid and inducing analogous symptoms. Caspar advises that after death the body be left open, exposed to the air, as the odor of prussic acid disappears rapidly, while that of nitrobenzol is persistent. The diseases with which the poisoning may be confounded most readily are some forms of *apoplexie foudroyante*, and sudden failure of the heart's action. The diagnosis may, during life, be almost impossible. It has been asserted that stertorous breathing does not occur in prussic acid poisoning; but it has been present in several reported cases.* An autopsy, however, ought generally to enable the physician to determine whether the case has or has not been one of prussic acid poisoning, if the symptoms during life are known.

A curious case of temporary *hemiopia*,[23] apparently caused by the fumes of hydrocyanic acid, is reported.

The period at which death may occur after the ingestion of the poison is set down by Lonsdale at from one to fifty-five minutes; but a case has been observed by Hilton Fagge,[24] in which the fatal result was put off for at least an hour and a quarter after the ingestion of hydrocyanic acid. After death the body often presents a livid surface, bloated countenance, fixed glassy eyes with dilated pupils, and clinched fingers; sometimes it offers nothing worthy of note except excessive rigidity, and the face may be very pale. When opened, the odor of prussic acid is generally, but not always, emitted; the mucous membrane of the stomach is very commonly found much congested, and the dark or cherry-colored liquid blood usually everywhere fills up the veins. The heart is soft and flaccid.

The treatment of poisoning by prussic acid is of little avail. Of the several chemical antidotes which have been proposed, hydrogen dioxide is the most practicable.† But such is the rapidity of absorption that the

* See *Taylor's Medical Jurisprudence*, Philadelphia, 1873, 363.

† See E. Merck, *Merck's Arch.*, 1900, ii. 94.

case is usually terminated before the antidote can be obtained. The asserted physiological antagonism of atropine has been disproved by Keen[25] and by Boehm and Knie. The stomach should, if possible, be emptied or washed out with a thirty per cent. hydrogen dioxide solution if at hand, and the hypodermic use of atropine and strychnine as respiratory stimulants might be tried; the inhalation of the vapors of ammonia, and the free exhibition of ammonia by the mouth and by injection into the veins, may be practised. Artificial respiration has been found very successful by Preyer, and by Boehm and Knie, in animals, and should always be assiduously practised. Next to it in importance is the use of the alternate cold and hot douche, about a half of a small bucketful of cold water and the same quantity of very hot (115° F.) water being dashed upon the chest in rapid succession.

ADMINISTRATION.—The dose of the dilute prussic acid (ACIDUM HYDROCYANICUM DILUTUM, U. S.) is one to three drops (0.06–0.18 C.c.).

Potassium Cyanide (POTASSII CYANIDUM, U. S.) occurs in white, amorphous, opaque masses, having the odor of prussic acid and a taste of similar character, but somewhat alkaline. It is deliquescent, and readily soluble in water.

When potassium cyanide is taken into the stomach, the acids there present convert it into prussic acid, and the same change probably occurs, although more slowly, even when the salt is injected directly into the blood-vessels. The physiological, therapeutical, and toxicological properties of this salt are similar to those of prussic acid.* Death, however, does not occur so soon as when hydrocyanic acid has been taken, and insensibility is sometimes not manifested for several minutes. Five grains of the salt have caused death in several cases. The therapeutic dose is one-twelfth to one-tenth of a grain (0.005–0.006 Gm.).

Silver Cyanide (ARGENTI CYANIDUM, U. S.) is a white insoluble powder, which is used solely for making prussic acid.

Cyanogen Gas has been studied physiologically by B. Bunge.[26] He finds that it kills by paralyzing the centres of respiration, but that it is less powerful and strong in its influence than is hydrocyanic acid, and causes only very feeble convulsions.

VEGETABLE ACIDS.

Although most of the official vegetable acids differ so much from the other substances considered in the present class as not to be poisonous except in enormous doses, and although they are never used to produce a profound impression upon the circulation, yet, since they have, or at least are believed to have, the power of lowering the force of the cardiac movements to some extent, and since they are so commonly believed to have a tendency to depress animal temperature as to be usually spoken of as *refrigerants*, the present seems to us a fitting place for their con-

* Poisoning has occurred from the inhalation of the vapors of the cyanide and from absorption through the hands (*Brit. and For. Med.-Chir. Rev.*, July, 1876, 231).

sideration. In experiments made by W. H. Gaskell,[1] similar to those described in the article on digitalis (see page 300), it was found that while alkalies contracted the arterioles of the frog, acids* caused a dilatation, probably by paralyzing the muscular coats. Acids also diminished the activity and power of the frog's heart.

ACIDUM TARTARICUM—TARTARIC ACID. U.S.

Tartaric acid occurs in large, hard, transparent, six-sided prisms, which are pyro-electric and phosphorescent when rubbed in the dark, are nearly free from odor, have a very sour taste, and are very soluble in water. In the shops the acid is almost always kept in the form of powder. Tartaric acid is the acid of the grape, and occurs in grape-juice as potassium bitartrate. When the juice undergoes fermentation and alcohol is developed, the acid salt, not being soluble in the newly formed menstruum, precipitates, collecting as a dark mass in the wine-casks, whence it is sent into commerce under the name of *argol* or *tartar*.

PHYSIOLOGICAL ACTION.—In powder or concentrated solution tartaric acid is a very decided irritant, capable of producing, when taken internally, violent œsophageal and gastric burning, vomiting, and, it may be, fatal gastro-enteritis.†

Mitscherlich states that three or four drachms suffice to kill a rabbit, the evident symptoms being great weakness of the heart's action, difficult and slow breathing, and steadily increasing pains, with slight convulsions before death. According to Devergie, it requires nearly half an ounce to kill a dog when given by the stomach; but Pommer (quoted by Husemann) asserts that one gramme (15.34 grains) injected into the crural vein of a dog will produce death.

Concerning the action of therapeutic doses of tartaric acid we have no definite information. General clinical experience, in accord with the experiments of Bobrick,‡ who found that very large doses render the heart's action weaker and slower, indicates that the drug is a very feeble cardiac depressant. It is probably partially burnt up in the body and partially eliminated by the kidneys. Wöhler,‡ in his experiments, found it in the urine in the form of calcium tartrate, while Buchheim‡ and Piotrowski‡ could find only a very small percentage of the ingested acid in the urine, and conclude that it is mostly destroyed in the body. Münch[1] finds that when tartaric acid or citric acid is given it soon appears in the urine. H. Bence Jones[2] has found that both citric acid and tartaric acid cause a pronounced increase in the acidity of the urine of persons taking them, and are apt also to give rise to the presence of free uric acid in the excretion. Unfortunately, Jones did not attempt to determine whether the increased acidity was or was not due to the presence of the vegetable acid in the urine.

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* Lactic acid, however, appears to have been the only one used, and it does not seem certain that the results of experiments would be the same with all acids, as is stated in Gaskell's generalization.

† Case reported in the *Brit. Med. Journ.* for June, 1893, in which the supposed dose was one hundred and eighty grains. Symptoms: diarrhœa, violent abdominal pains becoming more and more marked, followed by fever, delirium, and death on the seventh day. At the autopsy violent inflammation of the whole of the gastro-intestinal tract was found.

‡ All these are quoted by Husemann (*Die Pflanzenstoffe*). We have not seen the originals.

THERAPEUTICS.—Tartaric acid is rarely used in medicine, citric acid almost always being preferred. It may, however, be employed whenever it is desired to render the urine acid, in doses of ten to twenty grains (0.6–1.3 Gm.).

TOXICOLOGY.—There are, we believe, but three fatal cases of tartaric acid poisoning on record: one reported by Devergie,[3] one by Taylor,[4] in which death took place nine days after the ingestion of an ounce of the poison dissolved in half a pint of water, and one[5] in which half an ounce of the acid was *supposed* to have been taken. The treatment of tartaric acid poisoning consists in the free exhibition of magnesia, of lime, of potassium or sodium carbonate, or of any article, such as soap, containing an alkali in a suitable shape, which may be at hand. The after-treatment is that of toxic gastro-enteritis.

ACIDUM CITRICUM—CITRIC ACID. U.S.

Citric acid is the acid of lemon- and lime-juice. It occurs in rhomboidal prisms, of a sour almost corrosive taste, extremely soluble in water.

PHYSIOLOGICAL ACTION.—Citric acid in concentrated form is actively irritant, but, according to Mitscherlich, is less so than tartaric acid, since its concentrated solution has no action upon the sound skin. We know of no cases of fatal poisoning by citric acid, and it is very doubtful whether it is capable of causing death in man.

Piotrowski (quoted by Husemann) took, in six hours, thirty grammes, an hour later fifteen grammes, and an hour later thirty grammes, or nearly two ounces and a half in all, with the induction of no more serious symptom than vomiting.

Hugo Schulz[1] states that citric acid is an active antiseptic, a five per cent. solution being sufficient to preserve small pieces of meat for two weeks; one part in a thousand was fatal to paramecia.

THERAPEUTICS.—Citric acid is rarely itself employed in medicine. *Lemon-juice* (SUCCUS LIMONIS, U. S.) has been thought to be dependent upon potassium citrate for much of its virtue, but it contains, as shown by the analysis of H. Bence Jones,[2] in every ounce twenty-six or twenty-seven grains of free citric acid and not two grains of potassium citrate. Moreover, neither citric acid nor its salt acts in disease as does the fruit-juice.

Lemon-juice has several very distinct uses in medicine, all of them resting upon clinical rather than physiological data. The chief and most important of these is in the cure and prevention of *scurvy*. During the disease three to four ounces may be given three times a day. As a prophylactic against the disease, lemon-juice is simply invaluable; but it is absolutely necessary that it be of good quality. It may be prepared for long voyages in one of two ways: first, boil the juice slightly, strain, allow to cool, pour into bottles up to their necks, fill the vacant space above with pure olive oil, cork tightly, and keep the bottle upright;

second, add ten per cent. of brandy, and bottle as before. In *acute rheumatism*, benefit may be derived from the free use of lemon-juice, as originally proposed by Rees, of London. One or two ounces of it may be given four or five times a day ; but it is certainly less efficacious than the alkalies. In *catarrhal jaundice* and in habitual *torpor of the liver* the free administration of lemon-juice often aids in effecting a cure. In *fevers*, lemonade is a very refreshing and useful refrigerant drink.

ACETUM—VINEGAR.

The physical properties of vinegar are too well known to need description here. That best suited for medicinal use is in this country prepared from cider, and should have a trace of the taste of cider. Vinegar may be substituted for lemon-juice as the basis of an acidulous drink in fever when the lemon-juice is not to be had ; but as an *antiscorbutic* it is certainly very much inferior to it, and has not, that we are aware of, been tried in *rheumatism*.

Acetic Acid (ACIDUM ACETICUM, U. S.) is a colorless liquid, having a pungent odor, free from empyreuma, and an intensely acid, corrosive taste. It contains thirty-six per cent. of the monohydrated acetic acid, and has a specific gravity of 1.047. *Glacial* or *Absolute Acetic Acid* (ACIDUM ACETICUM GLACIALE, U. S.) is now official. It is a colorless liquid, crystallizing at 59° F., remaining solid at temperatures below 60° F., and actively escharotic,—in a measure, no doubt, owing to its properties of dissolving gelatin and gelatinous tissue and of effecting a partial solution of albuminous matters. *Dilute Acetic Acid* (ACIDUM ACETICUM DILUTUM) is officially prepared by the addition of five parts of water to one part of acetic acid, and should have the specific gravity of 1.008.

Dilute acetic acid or its equivalent, vinegar, acts upon the skin as a powerful stimulant and astringent, causing contraction of the vessels and great whiteness, so that it is often very useful as a topical application in various forms of *dermatitis*, especially *sunburn*, and also in *bruises* and *sprains*. We have found it, diluted with from one to four parts of water, a very grateful drink in *hæmatemesis*, and very effective in arresting the flow of blood. Diluted with two or three times its bulk of water, it is occasionally employed as an injection against *seat-worms ;* but the infusion of quassia is preferable.

The use of acetic acid as a caustic will be spoken of under the heading of Escharotics.

TOXICOLOGY.—Acetic acid in any of its more concentrated forms is a corrosive poison, and death has been produced by it in at least one case (Orfila[1]). The symptoms resemble those caused by mineral acids, and the treatment is exactly similar,—neutralization by an alkali or its carbonate, or by some substance, such as soap, containing an alkali, and the meeting of indications as they arise.

Oxalic Acid (ACIDUM OXALICUM) has been asserted[1] to be a va[1]

emmenagogue, but it is chiefly known to the profession as a poison. In 1874 Rabuteau[2] announced that in oxalic acid poisoning the nerves and muscles are not affected, and that therefore the acid acts upon the nerve-centres. This has been confirmed by the elaborate researches of R. Kobert and B. Küssner,[3] who find that it paralyzes the respiratory, vaso-motor, and other motor spinal centres. It is also a cardiac poison, arresting the heart in systole.[4] The acid is eliminated by the kidneys. As a poison, oxalic acid figures in two forms: that of simple oxalic acid, and that of the *acid potassium oxalate*, or *salt of sorrel*, or *essential salt of lemons*, as it is variously termed in common parlance. The symptoms produced are a hot acrid taste experienced during the swallowing, a burning in the gullet, soon extending to the stomach, intense abdominal pain, vomiting of highly acid, greenish, blackish-brown or bloody mucus (rarely of arterial blood), collapse, livid surface, cold skin, entire prostration of strength, small, irregular pulse, stupor, unconsciousness, sometimes convulsions,[5] and finally death. In some cases the gastric symptoms are very prominent; in others they are nearly wanting, and the chief manifestations are collapse and such nervous symptoms as almost complete general paralysis, numbness, and finally stupor; indeed, the patient may suddenly fall unconscious immediately after the ingestion of the poison.[6] In pregnant women abortion or at least death of the fœtus usually occurs. According to Taylor, the smallest quantity which is known to have caused death is one drachm. An ounce usually proves fatal, but has been recovered from. After death the coats of the stomach are found softened and swollen, and sometimes perforated.[7] Rabuteau affirms that the blood is everywhere scarlet; but this is certainly not always the case (Taylor[8]). In 1879 Kobert and Küssner discovered that oxalic acid will produce in the lower animals not only oxaluria and albuminuria with tube-casts, but also glycosuria.* In 1883 Sarganeck discovered sugar in the urine in human poisoning, and the recent investigations of Kobert have shown that in rabbits and cats even non-poisonous doses of the acid cause the appearance of a fermentable sugar in the urine. It would seem, therefore, that glycosuria should hold an important place among the diagnostic symptoms of the poisoning. According to Kobert and Küssner, a pathognomonic post-mortem lesion is the incrustation of the urinary tubules with crystals of oxalates. In poisoning by oxalic acid, the immediate administration of an antidote is of the utmost importance. As the potassium and sodium oxalates are poisonous, neither potash nor soda is available; but, fortunately, lime or chalk is a perfect antidote to oxalic acid, forming the excessively insoluble calcium oxalate. As time is a matter of so much importance, very often it is best simply to scrape "whitewash" off a wall, a ceiling, a fence, or wherever it may be at hand, rub it up hastily with water, and administer it freely. The after-treatment is that of toxic gastro-enteritis.

* Kobert has made the very important observation, that the extract of *Syzygium jambolanum* will control the glycosuria produced by oxalic acid.

As an emmenagogue, oxalic acid has been used in all forms of *amenorrhœa* with asserted great success. It is said also to be an active abortifacient, but as such is certainly extremely dangerous. The dose usually given is half a grain three or four times a day, but F. W. Talley has reported serious poisoning as produced by this amount.

Oxalic acid is a powerful germicide. According to O. Loew,[9] the one per cent. solution of the neutral potassium oxalate is very active in the destruction of infusoria, whilst Howard A. Kelly[10] asserts that potassium permanganate and oxalic acid afford the only known practical method of perfectly disinfecting the hands of the surgeon.*

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* The exact method practised by Kelly is as follows: 1. Scrubbing the hands, with especial attention to the nails,—not more than one millimetre in length,—for ten minutes in water frequently changed, at about 40° C. (104° F.). 2. Immersion of the hands in a solution of potassium permanganate, made by adding an excess of the salt to boiling distilled water, until every part of the hands and lower forearms is stained a deep mahogany red or almost black color, followed by transfer to a saturated solution of oxalic acid until completely decolorized and of a healthy pink color. This decolorization is accompanied by a sense of warmth, due to chemical reaction, and a sharp stinging wherever there is any abrasion of the epidermis. 3. Washing off the oxalic acid in warm sterilized water.

ORDER III.—NUTRIANTS.

FAMILY I.—ASTRINGENTS.

ASTRINGENTS are those drugs which cause contraction of living tis-
That they do not act, as has been supposed, either by coagulating
ain or by calling into action the muscular function is demonstrated
e transitoriness of their effects, and by the fact that they influence
containing no muscular fibre. Every living soft tissue appears to
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, in the other to have its tonicity increased, or to be astringed.
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ORDER III.—NUTRIANTS.

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ASTRINGENTS are those drugs which cause contraction of living tissues. That they do not act, as has been supposed, either by coagulating albumin or by calling into action the muscular function is demonstrated by the transitoriness of their effects, and by the fact that they influence tissues containing no muscular fibre. Every living soft tissue appears to possess a normal degree of condensation, which may be departed from on either hand : when this happens, in the one case the part is said to be relaxed, in the other to have its tonicity increased, or to be astringed. The action of astringents is always a *local one*,—*i.e.*, produced not through the intervention of the nervous system, but by direct contact with the part affected. A pure astringent should be capable of doing nothing beyond inducing contraction ; but in reality there is scarcely such a drug. Astringents are, when applied too freely, irritants.

The concordant experimental results reached by M. Rosenstein[1] and by R. Heinz[2] show that medium solutions of tannic acid, alum, and the salts of lead, zinc, iron, copper, and mercury contract the blood-vessels by a direct action. When, however, the solutions are too strong, according to Heinz, this contraction is followed by dilatation. Both experimenters state that the silver nitrate is the most powerful in its influence, producing an almost permanent contraction. According to Rosenstein, acids cause dilatation of the capillaries.

The clinical results obtained by the use of astringents in the treatment of inflammation can hardly be due to their action upon the blood-vessels, but seem to find more appropriate explanation in the discovery of Heinz, that, locally applied, they decidedly check the out-wandering of the white blood-corpuscles, probably, as he thinks, by modifying the wall of the blood-vessel.

The chief indication for the use of an astringent is the *existence of relaxation*. Local relaxation is commonly due to previous over-excitement. Thus, a throat is relaxed after over-use, or after inflammation.

Astringents are more efficient as local than as general remedies, but in cases of inflammation care must be taken to use them in such a way that they shall not act as irritants. Applied too soon or too vigorously, they may do harm. These remarks are scarcely applicable to some of the mineral astringents, such as lead and silver nitrate, which really

appear to have sedative properties, and may with care be used advantageously in all stages of inflammation, whenever there are distention and relaxation of the blood-vessels, although the general action of the part be that of nutritive excitement.

Closely allied to relaxation is *over-secretion*, and astringents are constantly used to *check morbid discharges*. Indeed, these discharges are often simply the result of relaxation. Thus, Asp has experimentally proved that division of the intestinal nerves and consequent paralysis and relaxation of the vessels are followed by free watery secretion. In such cases the indication for astringents is very plain. But when a morbid discharge represents a high degree of inflammation, the same care must be practised in the use of astringents as in treating other local inflammations. Especially is this true since free secretion is often nature's method of relieving local inflammation. Thus, when abnormal alvine discharges are dependent upon intestinal relaxation, astringents are most valuable, but when they are dependent upon *enteritis* or *colitis*, astringents may do harm.

If the morbid discharge by its profuseness endangers life, as in *serous diarrhœa*, astringents are urgently demanded. Very rarely, if ever, are these discharges other than paralytic in their origin ; even, however, if they be due to over-action, an astringent may be necessary to check their excessiveness.

Another indication for the use of astringents is to *check hemorrhage*, and the same general reasoning is applicable to this as to the other indications. Hemorrhage dependent upon over-action demands other treatment than by astringents. Sometimes in these cases it is necessary, however, to check the hemorrhage at all hazards, and then astringents may be used in conjunction with other measures, although they may be to some extent contra-indicated. Some of the astringents are employed locally to check hemorrhage due to traumatic or other ruptures of vessels. In such cases the astringents are employed as *styptics*, and do not act so much by their astringency as by coagulating the albumin of the blood and thus forming a clot and mechanically arresting the flow.

Under certain circumstances there seems to be a general relaxation or loss of tone throughout the whole system, which may be best met by a consentaneous use of tonics and astringents.

VEGETABLE ASTRINGENTS.

The active principle of the vegetable astringents is tannic acid, and as it is almost their sole therapeutic principle and represents them very closely, it seems proper first to consider it, and afterwards to point out any especial therapeutic virtues the crude drugs of the class may possess.

ACIDUM TANNICUM—TANNIC ACID. U. S.

There are two generic varieties of tannic acid, the *gallo-* and the *kino-tannic :* of these the former yields, upon exposure to the air in a moist

state, *gallic acid*, the latter a *gelatinous*, *inert* substance. They are further distinguished by the color of the precipitates which they yield with the persalts of iron ; gallo-tannic acid producing a blue-black, kino-tannic a green-black color.

The official tannic acid—the gallo-tannic acid—is obtained by treating powdered galls with washed ether, which on standing separates into two strata, the upper of which is ethereal and contains chiefly the coloring-matter and other impurities. The lower watery stratum contains the tannic acid, which is recovered by evaporation.

Commercial tannic acid is a light, feathery, *non-crystalline* powder, of a yellowish-white color, a faint odor, and an astringent, somewhat bitter taste. When absolutely pure, it is colorless and free from odor or taste other than that of astringency. Its reaction is strongly acid, and it unites freely with both organic and inorganic bases. It is very freely soluble in water, even more so in glycerin, somewhat so in dilute alcohol, scarcely at all in absolute alcohol, and not at all in ether free from water. With salts of the alkaloids it produces a whitish precipitate, very soluble in acetic acid ; with persalts of iron, a black (bluish or greenish) precipitate ; with lime-water, a precipitate which is at first whitish, then gray, dingy greenish, and finally brownish ; with gelatin or albumin, a whitish coagulum. All of these secondary products are tannates.

Physiological Action.—Applied locally, tannic acid is a very powerful astringent, causing contraction, and, in the case of a mucous membrane, great dryness. Sometimes, when it is used very freely, its irritant influence seems to overcome its astringent action, and we have seen diarrhœa result from its administration. Several experimenters (Rosenstein,[1] Fikentscher[2]) have denied that it causes contraction of the blood-vessels, because when they applied it to the exposed mesentery of a "Cohnheim frog," stasis of the blood, with dilatation of the vessels, not preceded by contraction, occurred. Daniels,[3] however, using rabbits, obtained different results, and Lewin has shown that the method of experimentation is faulty. Clinical experience abundantly proves that tannic acid applied to relaxed mucous membranes affects their whole substance.

Tannic acid coagulates albumin with so much avidity that it has been supposed to be incapable of absorption, but the very elaborate investigations of Lewin[4] cast much doubt upon the older views on this subject. Thrown rapidly into the blood, it undoubtedly causes a fatal thrombosis ; but Lewin asserts that when it is injected slowly and in moderate quantities the resulting albumin tannate is held in solution by the alkaline carbonates. He has also discovered that while tannin, in five per cent. solution, precipitates peptones out of watery solution, it is powerless in the presence of hydrochloric acid. Assuming the correctness of the investigations of Lewin, it is plain that tannic acid, when put in the stomach in small doses, must to some extent be absorbed unchanged. Lewin also asserts that it is, at least in part, elimi-

nated unaltered, as he has frequently recovered it from the urine. At the same time it seems very probable that most of the tannic acid is converted into gallic acid, either in the stomach before absorption or subsequently in the system, since in the viscera of a rabbit poisoned with it, Schroff[5] found only gallic acid; and according to Clarus,[5] the greater part of ingested tannic acid can be recovered from the stools as albumin tannate or as gallic acid. The recent researches of Stockman[6] afford a possible reconciliation of the results of Lewin with those of the older observers. Stockman finds that when tannic acid is given to the lower animals only a trace of it appears in the blood, while gallic acid can be obtained in abundance from the urine, with occasionally a small amount of tannic acid. If, however, sodium tannate be given, tannic acid appears in abundance in the urine, with a little gallic acid. The explanation offered by Stockman of this is probably correct,—namely, that tannic acid is usually converted in the stomach into an albuminous tannate, which is dissolved with great difficulty in the intestinal juices, so that time is afforded for the conversion of the tannic into gallic acid, whereas an alkaline tannate is absorbed at once and rapidly eliminated unchanged. When tannic acid is exhibited in medicine it is in all probability almost entirely converted into gallic acid. Wöhler and Frerichs have also found gallic acid with pyrogallic acid in the urine after the exhibition of tannic acid. Whether it acts chiefly as tannic or as gallic acid, it seems after absorption to exert marked astringent powers. Lewin has shown that in frogs poisoned with it the muscles are shortened and narrowed, and when loaded stretch less and recover their original length more nearly than do normal muscles. Küchenmeister[7] and Hennig state that in poisoned cats the spleen is notably diminished in size and increased in firmness; and Lewin has found in rabbits that tannic acid causes primary arrest of the urinary secretion, followed by a marked increase of the flow.

THERAPEUTICS.—As tannic acid undergoes in the system partial conversion into gallic acid, the latter is to be preferred to it when the part to be acted on can be reached only through the circulation. As a local application, tannic acid is much more powerful than gallic acid. Locally applied, it may be used to *overcome relaxation*, as in *spongy gums*, *mercurial sore mouth*, *hemorrhoids*, and *chronic sore throat*. To *check hemorrhage* it may be used whenever the source of the flow can be reached directly, as in *epistaxis*, *hæmatemesis*, *hemorrhage from the bowels*, etc. To arrest *excessive secretion* it may be employed locally in *leucorrhœa*, *diarrhœa*, *old abscesses*, *chronic ulcers*, *excessive perspiration*, *osmidrosis*, and various diseases of the skin. It is also often very useful for the purpose of hardening parts exposed to friction, as in cases of *sore nipples* and *tender feet*.

TOXICOLOGY.—Tannic acid can scarcely be called poisonous; although Rollett reports the case of a young girl in whom a very large quantity of it induced severe gastric and abdominal pains, with obstinate vomiting

and constipation, fever and general malaise. Both Schroff and Judell assert that eighty grains of it cause no symptoms of importance in the rabbit.

As an *antidote* it is useful in tartar emetic poisoning, forming an insoluble antimony tannate. It is also the best chemical antidote for the poisonous alkaloids; but, as the compounds it makes with them are slowly dissolved by the fluids of the alimentary canal, it must always be followed by emetics and cathartics.

ADMINISTRATION.—When given to act on the stomach, as in hæmatemesis, tannic acid should be in powder, ten to twenty grains (0.6–1.2 Gm.). When the bowel is to be influenced, as in diarrhœa, the drug should be administered in pill, three to five grains (0.2–0.3 Gm.), so that, if possible, it may pass the pylorus undissolved. For local use the glycerite of tannic acid (GLYCERITUM ACIDI TANNICI, U. S., twenty per cent.) may be employed, or the ointment (UNGUENTUM ACIDI TANNICI, U. S., twenty per cent.), or the troches (TROCHISCI ACIDI TANNICI, U. S., one grain each). Tannic acid enters into styptic collodion (COLLODIUM STYPTICUM, U. S., twenty per cent.).

A preparation of tannic acid which has come into notice since the last revision of the U. S. Pharmacopœia, and is not yet official, is TANNALBIN, a *tannin albuminate* proposed by Gottlieb, which contains about half of its weight of tannin. It is a light brown powder, insoluble in water or the gastric juice, tasteless, odorless, and not at all irritant to the mucous membrane. As a local application externally it is too feeble to be of value. When taken internally it probably is decomposed in the intestines and tannic acid slowly liberated; certainly we have used it with the utmost satisfaction, and believe it to be an extremely valuable remedy in the treatment of *chronic catarrh* or other condition of the intestines with relaxation and excessive discharge. We have never seen any evidences of irritation of the stomach or disarrangement of digestion caused by it. It has been strongly recommended by certain clinicians in *chronic Bright's disease* with great loss of albumin. Dose, fifteen to thirty grains (1–2 Gm.) three to six times a day, in powder or capsule.

ACIDUM GALLICUM—GALLIC ACID. U.S.

Gallic acid is a white, powdery substance, in fine acicular prisms, soluble in one hundred parts of cold water, in three parts of boiling water, and freely soluble in alcohol and in ether. Its taste is acidulous and astringent.

According to the usual method, gallic acid is prepared by the exposure of moistened powdered nutgalls in a warm place for a month. A species of fermentation, with the development of a peculiar fungus, is said to occur, during which oxygen is absorbed, carbonic acid is evolved, and glucose and gallic acid are produced. M. Sacc[1] has, however, denied this, affirming that the change is simply one of hydration, tannic acid

being an anhydride of gallic acid. Tannic acid also may rapidly be converted into gallic acid by the action of dilute sulphuric acid.

Gallic acid produces with persalts of iron a bluish precipitate, with lime-water a whitish precipitate, changing to blue and then to violet or purplish,—all of these precipitates being gallates. It does *not coagulate gelatin* or *albumin*, and is, therefore, not a styptic. As an astringent it is less powerful than tannic acid. It escapes from the body through the kidneys.

THERAPEUTIC ACTION.—Gallic acid is not nearly so efficient as tannic acid, when applied locally, but should always be preferred when the part is to be reached through the medium of the circulation. It is useful as an astringent in *hæmoptysis*, *hæmaturia*, *colliquative sweats*, etc. It has been recommended in *bronchorrhœa* and in the profuse expectoration of *chronic phthisis*. In our hands, however, it has completely failed in the latter affections. In *Bright's disease*, when there is an abnormally large secretion of highly albuminous urine, it may lessen very materially the excretion of albumin.

ADMINISTRATION.—The dose of gallic acid is ten to thirty grains (0.6–2 Gm.) in capsules or powder, repeated *pro re nata*.

GALLA—GALLS. U. S.

Galls are vegetable excrescences which are produced by the deposition of the ova of insects. They occur on almost all kinds of plants, even on fungi, but the official gall is developed on the Quercus lusitanica by the act of the fly Cynips gallæ tinctoriæ. There are in commerce two varieties of galls, derived chiefly from the Levant. The *blue* or *green galls* are globular, solid bodies, from the size of a pea to that of a hickory-nut, externally smooth, or more commonly marked with large tubercles. They are the young galls which have been gathered before the ova of the fly have hatched, or before the caterpillar has eaten out the interior of its birthplace. The *white galls* are large, light, hollow bodies, with a hole, through which the Cynips has escaped after having fed upon the interior during its whole larval life. They contain but little tannic acid, and are of comparatively little value.

THERAPEUTICS.—The sole value of galls is as the source of tannic acid. As galls, they should not be used in medicine; the tincture (TINCTURA GALLÆ—twenty per cent., U. S.) and the ointment (UNGUENTUM GALLÆ—twenty per cent., U. S.) are still sometimes used.

CATECHU—CATECHU. U. S.

An extract of the wood of an East Indian tree,—the Acacia Catechu. It occurs in masses of various shapes, or in small fragments, of a dull reddish-brown color, and having a bitterish, astringent, and, after a time, sweetish taste. It contains kino-tannic and catechuic acids. *Pale catechu*, or *gambir*, which is official in the British but not in the United States Pharmacopœia, occurs in small cubes, about an inch in diameter, lighter

than water, pale yellowish within, deep yellowish or reddish brown externally. Catechu is a powerful astringent. Dose, for *diarrhœa*, twenty to thirty grains (1.5–2 Gm.). Dose of compound tincture (TINCTURA CATECHU COMPOSITA—ten per cent., U. S.), one to three fluidrachms (4–12 C.c.); troches (TROCHISCI CATECHU, U.S.), one grain each.

KINO—KINO. U.S.

The inspissated juice of Pterocarpus marsupium and of other trees. It occurs in small, irregular, angular, shining, reddish, brittle fragments, of a bitterish, highly astringent, and, after a time, sweetish taste. There are four varieties,—the East India, West India, Botany Bay, and African. Of these, the first is common, the second rare, and the last two are never seen in our market. Kino contains kino-tannic acid, and in its therapeutic powers is almost identical with catechu. Dose, twenty to thirty grains (1.5–2 Gm.); of a tincture (TINCTURA KINO—ten per cent., U. S.), one fluidrachm (4 C.c.).

HÆMATOXYLON—HÆMATOXYLON. U.S.

The heart-wood of Hæmatoxylon Campechianum, or logwood-tree, a native of Central America,—a dense, heavy wood of a deep reddish-brown color, containing, besides kino-tannic acid, a crystalline principle, *Hæmatin* or *Hæmatoxylin*, which when pure is yellow, but readily yields red or purple dyes. According to F. Combemale,* hæmatoxylin is capable of causing a fatal intoxication, commencing with rigors and fever and ending in vomiting, anuria, coma, and collapse.

Hæmatoxylon is a mild, efficient astringent, valued on account of its sweetish taste. It is readily taken by children, but is sometimes objected to on account of the staining of the diapers by the blood-red stools which it produces. Dose of extract (EXTRACTUM HÆMATOXYLI, U. S.), ten to thirty grains (0.65–2 Gm.).

The following formula offers an efficient and elegant remedy for *diarrhœas* of relaxation; the proportions may be varied to suit individual cases. ℞ Ext. hæmatoxyli, ʒii; Acid. sulph. aromat., fʒiii; Tinct. opii camph., fʒiss; Syrupi zingiberis, q. s. ad fʒvi. M.—Dose, a tablespoonful, properly diluted.

KRAMERIA—RHATANY. U.S.

The roots of Krameria triandra, a native shrub of Peru, and of Krameria Ixina, a shrub growing in Colombia, British Guiana, and Northern Brazil. This woody root, as it occurs in our markets, varies from one-fourth of an inch to one inch in diameter, and from half a foot to three feet in length. The readily separable bark is of a deep reddish color. The internal woody portion is of a lighter hue, although decidedly reddish. The bark contains a much larger percentage of the active principle, kino-tannic acid, than the wood. Rhatany is a powerful

* *Bull. Gén. de Thérap.*, 1894, cxxvii.

astringent, similar in virtue to kino and catechu, but is never administered in powder. Dose of the extract (EXTRACTUM KRAMERIÆ, U. S.), five to ten grains (0.3–0.6 Gm.); of the tincture (TINCTURA KRAMERIÆ—twenty per cent., U. S.), half to one fluidrachm (2–4 C.c.); of the fluid extract (EXTRACTUM KRAMERIÆ FLUIDUM, U. S.), twenty minims (1.25 C.c.).

QUERCUS ALBA, U. S., and QUERCUS TINCTORIA are the inner barks of the trees whose names they bear,—the *white* and the *black oak* respectively. The latter is a rough, yellowish-brown bark, which is used in dyeing, under the name of *quercitron*. On account of its imparting readily its color, it is rarely, if ever, employed in medicine. White oak bark also stains, but not nearly so deeply as does black oak bark, and, containing a large percentage of gallo-tannic acid, is used as a means of making cheap astringent infusions for baths, vaginal washes, etc., also in powder for poultices.

ROSA GALLICA, U. S., is the dried petals of the half-opened flowers of the hundred-leaved rose. They are of a deep red color, of a pleasant scarcely astringent taste, and contain a small percentage of gallo-tannic acid, red coloring-matter, and a trace of volatile oil. Sulphuric acid changes their infusions or tinctures to a bright red color. They are almost destitute of therapeutic virtues, but their preparations, except the fluid extract, are used as elegant vehicles. The U. S. Pharmacopœia recognizes a fluid extract (EXTRACTUM ROSÆ FLUIDUM), a honey (MEL ROSÆ—twelve per cent.), a confection (CONFECTIO ROSÆ), and a syrup (SYRUPUS ROSÆ—fluid extract, 12.5 per cent.).

ROSA CENTIFOLIA, U. S., or *Pale Rose*, contains little tannic acid, with a volatile oil, and is used simply on account of its pleasant odor: out of it are prepared rose-water (AQUA ROSÆ, U. S.) and the very elegant, bland emollient ointment, cold cream (UNGUENTUM AQUÆ ROSÆ, U. S.).

GERANIUM, U. S., is the rhizome of Geranium maculatum Linn., an indigenous herbal plant. It occurs in pieces from one to three inches long, one-quarter to one-half inch in thickness, wrinkled, contorted, tuberculated, often fibrillated, brownish externally, grayish internally. The taste is a nearly pure astringent one. It contains a large percentage of gallic and tannic acids, and is a somewhat popular astringent. It may be boiled in milk for children needing a mild astringent. Dose, twenty to thirty grains (1.25–2 Gm.). Dose of the fluid extract (EXTRACTUM GERANII FLUIDUM, U. S.), thirty minims to a fluidrachm (2–4 C.c.).

RHUS GLABRA. U. S.—The fruit or berries of the sumach contain a very large percentage of tannic and malic acids. They are not used internally, but their fluid extract (EXTRACTUM RHOIS GLABRÆ FLUIDUM, U. S.) affords a very superior gargle in *anginose affections*. It may be

diluted with from two to four parts of water, and potassium chlorate added to saturation.

AGARIC.—Under the name of Agaric various species of fungi belonging to the genus *Boletus* have been employed from time to time in medicine. Of these the *white agaric*, or *purging agaric* of writers, is obtained from Boletus laricis, the fungus of the European larch. It contains a whitish, very bitter acid, variously known as *agaric acid*, or *agaricinic acid*, slightly soluble in cold water, moderately so in hot water. According to the researches of Hofmeister,[1] agaric acid has upon the lower animals very little influence except in arresting the secretion of sweat by paralyzing the peripheral nerves of the sweat-glands. Both the impure extract, known in commerce as *agaricin*, and agaric acid have been extensively used for the purpose of arresting *colliquative sweats*, and in our experience are valuable remedies. The only untoward effect ever produced, even by the largest dose, is irritation of the gastro-intestinal canal. Two to five grains (0.13–0.3 Gm.) of the agaricin may be given three times a day, commencing with the smaller dose and increasing. According to Hofmeister, the dose of the pure acid is from one-sixteenth to one-third of a grain (0.004–0.02 Gm.).

MINERAL ASTRINGENTS.

ALUMEN—ALUM. U.S. (POTASSIUM ALUM.)

Formerly the double salt of alumina and potassium constituted the ordinary alum as well as the official drug. Ammonia, as a secondary product in the manufacture of coal-gas, has become so cheap, however, that it is now used very largely instead of potassium, although the potash alum is alone recognized in our official standard. The two salts are identical in physical and medical qualities, but when the ammonia alum is triturated with lime the odor of ammonia is at once evolved. Alum occurs in octahedral colorless crystals, which are often aggregated into large masses. Its taste is astringent, acidulous, and sweetish. It is soluble in nine parts of water at 59° F. and in one-third part of boiling water. It is slightly efflorescent, and when heated parts with its water of crystallization and is converted into a white powder (ALUMEN EXSICCATUM, U. S., or *Dried Alum*). The alkalies and their carbonates, lime, magnesia and its carbonate, potassium tartrate, and lead acetate are incompatible with alum.

PHYSIOLOGICAL ACTION.—As alum, even in very dilute solutions, coagulates albumin, it would appear as though it could not be absorbed. Since, however, both George B. Wood and A. Stillé assert, on what authority we do not know, that alumina can be detected in the urine of persons taking it, it or its derivatives must find a way into the blood. What changes it undergoes in the alimentary canal, or in what form it enters the blood, is not known.

Applied to a tissue, it acts as a very powerful astringent and irritant. Orfila found that in dogs one or two ounces of it simply induce violent vomiting and purging, while in Mitscherlich's experiments two drachms of it produced in rabbits fatal gastritis, evidently on account of their inability to vomit. In man, large doses internally produce symptoms of violent gastric irritation. One ounce and five drachms of the burnt alum caused death in a man in eight hours.[1]

THERAPEUTICS.—Alum may be used locally to serve all the purposes of a very active astringent. It has been employed very frequently with success as a styptic to arrest hemorrhage; and, applied by the atomization of its saturated solution, we have found it of signal service in *hæmoptysis* and in *bronchorrhœa*. It also frequently enters into the composition of gargles for *sore throat;* but this practice is to be reprobated, since alum acts very destructively on the teeth. In *colliquative sweats*, sponging at bedtime with alum-water, or, still better, the taking of an alum-water bath, will often materially aid in restoring the lost tone to the skin. In *chronic ulcers* with exuberant spongy granulations, and in certain conditions of *conjunctivitis*, alum curd is often applied with benefit. When it is desired to exert an astringent action upon the internal organs, alum is not nearly so useful as other members of the class.

Owing to its irritant properties, alum when given in sufficient amount acts as a mechanical emetic, but is too uncertain in its action to be of much value.

So long ago as the last century, Grashius, of Holland, commended alum in *colica pictonum*, and, although for a long time its value was not recognized, abundant confirmative testimony has recently been brought forward. Since it is a soluble sulphate, it is of course a chemical antidote to any lead salt which may be in the alimentary canal. It is, however, of service when there is no lead in the primæ viæ, and must act in some way as yet unknown. It has, indeed, been used with asserted success in other neuroses of the alimentary canal,—in *gastralgia* and in *intestinal neuralgia*. Aldredge even commends it in *habitual constipation*. Dried alum is sometimes used as a very mild escharotic for the destruction of exuberant granulations in ulcers.

ADMINISTRATION.—An astringent dose is from ten to twenty grains (0.6–1.2 Gm.); an emetic dose, a teaspoonful of the powder for a child, a tablespoonful for an adult, in syrup. Dose, in *colica pictonum*, twenty to forty grains (1.2–2.5 Gm.) every three or four hours, combined with morphine. *Alum curd* may be made by dissolving two drachms in a pint of milk, and straining, or by rubbing the alum with white of egg.

PLUMBUM—LEAD.

When a soluble salt of lead is applied to a part in not too concentrated solution, it acts as an astringent and sedative. Owing to the contraction of the vessels which is induced, the tissue becomes blanched,

and any inflammatory action which may be present is remarkably affected. When in concentrated solution, the mildest preparations of lead are capable of acting as irritants, increasing or even originating inflammation. When the salts of lead are taken internally in therapeutic doses, no decided symptoms are generally induced, except a diminution of the secretions, especially of those of the alimentary canal. Sometimes, when full therapeutic doses are exhibited, a slight lowering of the frequency and force of the pulse* is said to result, but we have never witnessed this. The insoluble are much less irritant than the soluble lead preparations.

Toxicology.—Acute lead-poisoning is usually produced by a soluble salt, notably the acetate ;† but a case reported by Freyer[1] shows that white lead and other insoluble preparations may act as violent and even fatal irritant poisons. When the acetate is ingested in toxic dose, the first symptom is usually a persistent, sweet, somewhat metallic taste ; this in a few minutes is followed by vomiting, which may or may not be preceded by nausea. The matters vomited are often milky white, from the presence of lead chloride. A severe burning persistent pain in the abdomen now comes on, and is accompanied by a craving for drink. There may be obstinate constipation, or diarrhœa may ensue : in either case the stools are generally black from the sulphuret of lead. In certain cases a state of collapse is developed ; the pulse falls to 40 or 50 per minute, the voice is lost, the face is deadly pale, the lips are livid, and syncope seems imminent. In other instances the nervous symptoms may predominate, or they may accompany those of disordered circulation : cramps in the calves of the legs, severe neuralgic pains in the extremities, paralysis and anæsthesia, vertigo, stupor, may any or all of them be present. In fatal cases, coma, with or without convulsions, finally develops. A distinctive mark of lead-poisoning, which occasionally is present very early, is the blue line upon the gums. After death inflammation of the alimentary mucous membrane is sometimes, but not always, found. One ounce of lead acetate, subacetate, or nitrate may take life.

The treatment of *acute lead-poisoning* consists in the evacuation of the stomach, the exhibition of sodium or magnesium sulphate, and the meeting of the indications as they arise. The Epsom and Glauber's salts act as chemical antidotes, by precipitating the insoluble sulphate of lead, and also, if in excess, empty the bowel of the compound formed. To allay the gastro-intestinal irritation, albuminous drinks should be given and opium freely exhibited.

Subacute and chronic lead-poisoning are almost always accidental, and occur most frequently among those whose occupation exposes them to daily contact with some compound of the metal ; manufacturers of white lead, painters, glaziers, and similar artisans furnish the greater number

* See Laidlaw's Observations (quoted by Stillé), *Therapeutics*, second edition, i. 177.

† According to Husemann (*Handbuch der Toxicologie*), the *poudre de succession*, so famous during the reign of Louis XIV., was composed chiefly of lead acetate.

of victims. They may be seen, however, in persons of all conditions of life, for although neither food nor drink is often purposely adulterated with lead, yet it is frequently introduced into the system accidentally along with those necessities. Lead pipes are habitually used for the conveyance of water, and when the water contains salts of lime, even in minute proportion, no evil results, because through the decomposition which ensues insoluble coatings are deposited on the inside of the pipes.* When the water is pure, no such reactions occurring, the lead is slowly dissolved in the form of a carbonate, and poisoning may result. Poisoning has also frequently resulted from the employment of cosmetics and hair-dyes, from the internal or external medical use of lead preparations,[2] from cooking bread with painted wood,[3] from imperfectly burnt pottery,[4] from habitually biting silk thread which rascally manufacturers often load with lead to give weight to it,† from lead bullets retained in the body (Vucetió[5]), and in other curious ways.

That form of lead-poisoning in which colic is the most decided symptom is often spoken of as *subacute*. After some days of malaise and wretchedness, or sometimes very suddenly, the victim is taken with abdominal colicky pains, which increase in intensity until they become very severe. They are constant, with occasional exacerbations, are sometimes dull, sometimes sharp, are generally described as twisting, and seem to centre around the umbilicus. Very often there are repeated retching and vomiting. The walls of the abdomen are retracted, rigid, knotted; the bowels are obstinately costive; the tongue is contracted and whitish, the appetite gone, and the thirst sometimes excessive. Neuralgic pains in the thorax and in the extremities are of frequent occurrence. In some cases the conjunctiva is distinctly icteroid. This condition, which is known as *colica pictonum*, or *lead colic*, may after a time abate, and the patient convalesce; more usually, however, the attacks recur from time to time, becoming gradually less severe and distinctive, and the patient gradually passes into chronic lead-poisoning. Occasionally the colic increases in severity; sometimes the course of the disease is interrupted by various violent accidents.

The cases of *chronic lead-poisoning* vary so much in their symptomatology as almost to baffle concise description. It has seemed to us that the symptoms can best be studied by arranging the cases in groups, but it must be remembered that in nature not only do these groups shade into one another, but also that there are all kinds of mixed cases,—cases which offer simultaneously or successively symptoms of two or more of these various groups.

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* For an elaborate article on the chemical relation of water to lead, see *Schmidt's Jahrbücher*, cxliv. 279.

† Chronic lead-poisoning is produced much more frequently by insoluble than by soluble compounds of lead, and it is probable that any saturnine preparation may cause it. Thus, *lead chromate* has killed numbers of people. (See *Med. News*, ii. 1887; also *Therap. Gaz.*, iv.)

The first group contains the great bulk of cases of chronic lead-poisoning, at least as seen in this country. The symptoms consist of failure of health, more or less digestive disturbance, and double wrist-drop,—*i.e.*, paralysis of the extensor muscles of each hand. Not rarely, the only noticeable symptom is the wrist-drop, the general health seeming to be very good. The true nature of such cases can usually be at once recognized by the bilateral character of the wrist-drop, cerebral and pressure paralyses being almost invariably unilateral. We have seen, however, bilateral pressure palsy, and also one or two cases of unilateral plumbic wrist-drop, due to a local absorption of lead, in artisans who had one hand much of the time in a preparation of the metal. Similar cases have been recorded by Manouvriez.[6]* The wrist-drop may exist alone, but not rarely there is with it anæsthesia of the affected part, or sometimes of the shoulders or other unparalyzed portion of the body. When the paralysis is complete, the electro-contractility of the muscles is in great part or altogether absent.

The rarer forms of chronic lead-poisoning may be divided into the cerebral, the periphero-spinal, and the nutritive.

In the cerebral cases should be included those which are commonly spoken of as *encephalopathia saturnina*, or *saturnine cerebritis*.†

In cerebral cases of lead-poisoning the violent brain symptoms may develop with great suddenness, or may be preceded by some days of headache, giddiness, sleeplessness, disturbed vision, strabismus, tinnitus aurium, psychical aberration, or other prodromes of brain disturbance. Delirium, which is among the chief manifestations of the fully formed condition, may be mild, but is often maniacal ; stupor may replace or alternate with it ; and violent epileptiform convulsions, ending in coma, are not infrequent. These convulsions are usually the precursors of death, but recovery may occur even after the most severe symptoms.[8]

Without the development of such severe symptoms, headache, loss of memory, giddiness, somnolence, hemianæsthesia, disturbance of the special senses, aphasia, monoplegia, hemiplegia, or multiple cerebral palsies may occur during chronic lead-poisoning. Death, preceded by severe cerebral symptoms, may take place without organic lesion ; but usually, when focal symptoms have been present, localized alteration of brain structure, secondary to diseases of the cerebral vessels, or to chronic inflammation of the brain or its membranes, can be detected. Sometimes the cerebral symptoms are uræmic ; indeed, true plumbic encephalopathy and plumbic uræmia from contracted kidney may coexist. Again, the more serious affection may be masked by a saturnine hysteria, since cases have been reported by Charcot and by Dutil in which hysterical hemianæsthesia, amaurosis, anosmia, loss of sense of taste, and other cerebral symptoms have been the outcome of a major hysteria due to chronic lead-poisoning. Such cases as these probably occur only in individuals of previously hysterical temperament, and must be extremely rare in persons not of the so-called Latin race.

Disturbances of vision are so frequent and so marked in lead-poisoning as to deserve special mention. They have been classified by de Schweinitz as follows :

1. Transient amblyopia, without ophthalmoscopic change.

* See also *La France Méd.*, 1882, i. 829.

† George F. Crooke[7] reports a case in which lead plaster taken for the production of abortion caused not only miscarriage, but also fatal brain lesions, preceded by choked disks, albuminuria, and convulsions.

2. Amblyopia without fundus lesions, or with congestion of the nerve-head, and with central scotomas analogous to those caused by other toxic agents.

3. Optic neuritis, or neuro-retinitis, either specifically due to lead or secondary to changes in the brain or kidneys.

4. Optic nerve atrophy, either consecutive to a plumbic papillitis or retrobulbar neuritis, or due to a primary effect of the lead on the visual organ.

5. Various types of retinitis, vasculitis, and perivasculitis, either primarily due to lead or secondary to nephritis.

Strabismus from muscular paralysis is sometimes of saturnine origin.*

The second group of cases of chronic lead-poisoning consists of those in which the nerve-symptoms apparently originate below the cerebrum.

In the present group belong cases such as have been reported by Putnam, by Tisier, by Raymond, and by G. L. Walton, in which the phenomena resemble those of locomotor ataxia, except in the presence of tenderness over the nerve-trunks, preservation of the tendon reflexes, or some other atypical symptoms. We have seen several cases in which the symptoms resembled those of an acute poliomyelitis, consisting chiefly of wide-spread paralyses with rapid wasting of the muscles. These cases usually can be differentiated by the presence of violent neuralgic pains, paralysis of the bladder and rectum, or other atypical symptoms. Similar to these cases are those spoken of by G. Lyon,[9] in which a rapid general paralysis spread from part to part, until at last aphonia and dyspnœa, and even death from asphyxia, resulted. Severe intractable chorea has been produced by lead. Oscar Buber[10] calls attention to the form of irregular lead palsy in which the paralyzed muscles are affected with peculiar slow, worm-like, and occasionally painful contractions. Disturbances of sensation may occur in lead-poisoning; anæsthesias are, perhaps, not very rare, and violent neuralgic pains, probably due to neuritis, may be the chief manifestation. In a case of H. C. Wood's in which the diagnosis was confirmed by finding lead in the drinking-water and in the urine of the patient, the symptoms were intense general pruritus, with violent neuralgic pains shooting through the rectum and the urethra, coming on at night and producing an insomnia which appeared to be unconquerable. The lesion is often peripheral, and the very rapid pulse seen in some cases may be due to disease of the vagi, which Prevost and Binet[11] have found degenerated.

The third group of cases comprises those in which the poison chiefly expends itself upon glandular or visceral organs, or in producing wide-spread nutritive changes.

It would seem that almost any of the vital structures may undergo degeneration. Potain[12] reports a case of saturnine cirrhosis of the liver; while Valence[13] and Claisse and Dupré[14] call attention to plumbic parotiditis, which may take the form of a slowly progressive chronic hypertrophy of the gland, with dryness of the mouth, or of a distinct sclerosis, or there may be ulceration of the orifice of Steno's duct and obstruction. Rudolf Maier[15] has found in poisoned animals atrophic degenerations of the intestinal glands and walls, and there can be no doubt that similar alterations may cause emaciation and anæmia in human plumbism.

Of great frequency and importance are the lesions produced by lead in the kidneys. It must be remembered that temporary albuminuria may occur in lead-

* For discussion of details, see Beau (*Arch. Gén.*, 1848), Manouvriez (*Arch. de Physiol. Norm. et Patholog.*, 1870, 411; 1876, 762), A. De Cours (*De l'Hemianæsthesia saturnine*, Paris, 1875), Proust (*Progrès Méd.*, 1879, vii. 546), Debove (*Ibid.*, 99, 117), and Alex. Westphal (*Archiv für Psychiat.*, 1887–88, xix.).

poisoning without serious implication of the kidneys; while, on the other hand, fatal nephritis may exist when there is no albumin in the urine (Lancéreaux[16]). A persistent low specific gravity of the urine in lead-poisoning is a symptom of the utmost gravity. Geppert[17] confirms the observation, previously made by Olivier, that in temporary plumbic albuminuria many isolated kidney epithelial cells may often be found in the urinary sediments; and it is evident that a persistence of this condition must end in chronic renal disease. After death, which may be induced by uræmia, the kidneys are found contracted, granular, with excessive development of the fibrous tissue (followed by contraction) and great thickening of the walls of the blood-vessels: these changes are identical with those of contracted kidney produced by gouty and other irritant poisons. As Ellenberger and Hofmeister have shown that the lead is chiefly eliminated by the kidneys, the frequency of plumbic nephritis is easily explained; but it is not readily perceived why it is so frequently associated with an arthralgia whose course and lesions closely simulate those of chronic gout. Garrod (1859), Dickinson, Lancéreaux, Rosenstein, Leyden,[18] and other authors have reported so many cases of this association of renal and gouty manifestations that it can scarcely be doubted that the plumbism is the cause of the gouty symptoms, and not simply a complication of gout.*

There are certain cases of lead-poisoning which do not conform to any of the types as yet given.

Among these very irregular cases may be mentioned those reported by E. Levy,[19] in which acute asthma was produced by the inhalation of the dust of white lead. Again, chronic saturnine asthma is sometimes seen in feeble, narrow-chested people. James J. Putnam[20] calls attention to the fact that in lead-poisoning of children the legs and feet are commonly paralyzed. Pagliano[21] has reported a case of saturnine facial palsy. It has been abundantly proved both by clinical experience and by experiments made upon the lower animals that in chronic lead-poisoning the metal may pass through the placenta into the fœtus, causing its death, with subsequent abortion.†

As any of the obscure manifestations of lead-poisoning may exist, and even prove fatal, without a distinct history of other more characteristic phenomena, great care is sometimes necessary to avoid being misled, and not rarely the true nature of saturnine epilepsy or of saturnine albuminuria is overlooked. Hence the importance of the *blue line upon the gums where they join the teeth*, which is very common in persons suffering from lead-poisoning. It is said to be the result of a formation of lead sulphide in the walls of the capillaries. As was first pointed out by J. J. Putnam,[22] chronic lead-poisoning may exist without this blue line upon the gums. Under such circumstances, if the symptoms be obscure the diagnosis can be established only through a chemical examination of the urine.‡ The practitioner should see that the urine which is to be sent to the chemist for examination be slightly acidified, that directly after passing it be put in flint-glass bottles, and that it be at least a quart in

* Consult *Deutsch. Med. Wochenschrift*, 1883, 185, 351; 1884, 129; also Paul Musehold (*Die Bleivergiftung*, Berlin, 1883). We have ourselves seen one case.

† See Constantine Paul (*Archiv. Gén.*, 1860, xv.), Legrand and Winter (*Compt.-Rend. Soc. Biolog.*, 1889), and B. Annino (*Schmidt's Jahrb.*, ccxliv., No. 11).

‡ For an elaborate discussion, see leading article in *Therap. Gaz.*, Dec. 1887; *Ibid.*, iii. 813, and iv. 92.

quantity. From a diagnostic point of view an extremely important observation, if it be confirmed, is that of Deroide and Lecompt,[23] who assert that there is in the urine of saturnine patients *urohæmatoporphyrine*, a red pigment, soluble in ether, water, and alcohol, which can readily be recognized by the spectroscope.

In those cases of lead-poisoning which pursue a slow course to death the paralysis involves after a time the extensors of the lower as well as of the upper extremities, epileptic paroxysms occur at intervals, racking pains shoot through the limbs, points of cutaneous anæsthesia appear, and often albuminuria aids in producing the fatal issue. Gradually the patient becomes more and more cachectic, general œdema and the whitened skin betray the increasing anæmia, the paralysis extends from muscle to muscle, locomotion becomes impossible, and, if a convulsion or other accident do not close the scene, death at last takes place from loss of power in the respiratory muscles. Malassez[24] has found that in the anæmia of lead-poisoning the red globules are not only diminished in number but also increased in size. After death lead has frequently been detected in the tissues.

Heubel[25] found most of it in the bones, and less in the muscular than in the nervous system. Chatin[26] obtained from the cervical spinal cord three in one hundred and fifty parts. In the studies of Ellenberger and V. Hofmeister[27] the liver and kidneys were found to contain the most lead, after them the bones, then the nerve-centres, and finally the flesh. Prevost and Binet found the lead in all the tissues, but believe that it especially accumulates in the kidneys.* G. N. Pitt[28] reports finding over forty-seven grains of the lead sulphite in nine inches of the colon.

The electro-muscular contractility is affected very early in lead-poisoning, and may be lost before the voluntary movements. It is stated

* A question of the most serious importance, which at present we are not able to answer positively, is as to whether sclerosis, neuritis, and other chronic affections of the nervous system which have been reckoned as idiopathic or of unknown origin are not frequently the outcome of an entirely latent lead-poisoning. In a remarkable paper, J. J. Putnam, of Boston (*Trans. Assoc. American Physicians*, ii.), describes cases entirely apart from recognized types of lead-poisoning, in which the metal was found in the urine. These cases may be grouped as follows: 1. Trembling of hands; sense of coldness and numbness in toes; lancinating pains in legs; fatigue on exertion. 2. Marked progressive spastic paraplegia, with myosis and pupillary reactions; ataxia and some atrophy of hands. 3. Progressive weakness and stiffness in legs, with diffused and almost universal pains; marked tremor. 4. Temporary pain in chest, with slight dyspnœa; progressive numbness, heaviness, and weakness in legs. 5. Numbness in feet and legs, with impairment of strength; tremor of hands and tongue; some wasting of small muscles of hands; temporary retention of urine. Closely connected with this subject is the question whether lead may not be for a length of time in the system and appear in the urine without doing injury to the health. In a paper (*Boston Med. and Surg. Journ.*, 1890, cxxiii.) Putnam brings forward more facts, whose import is at present very doubtful. In an examination of the urine of sixty-eight persons, presenting no evidences of any disarrangement of health, lead was found in the proportion of about seventeen per cent., while the urine of thirty-six persons suffering from chronic and subchronic affection of the nerves, nerve-centres, and *spinal cord* contained lead in the proportion of fifty per cent. In the last group were cases of tremors with debility, of chronic multiple neuritis, multiple sclerosis, spastic paraplegia, muscular atrophy, epilepsy, sciatica, digestive disorders, etc. (*Bost. Med. and Surg. Journ.*, 1889, cxxi.). One cannot help suspecting that, owing to defective water-supply, Bostonians are especially prone to contain lead.

by M. Raymond that the short extensor of the thumb preserves its function when all the other extensor muscles are paralyzed. The paralyzed muscles are finally exceedingly wasted, and their structure may be so totally destroyed that scarcely a single striated fibre can be found. The nerve-trunks are lessened in size, in many of their tubules the medulla has been replaced by fatty granules, and in some cases every trace of the tubules has disappeared and the nerve has been reduced to a fibrous cord.

According to the researches of Dégérine,[29] the first appearance of change in a nerve-trunk consists in the myeline becoming broken up into blocks, and the nature of the change is a commingling of a parenchymatous and an interstitial neuritis, which both Dégérine and Vulpian have traced upward as far as the anterior spinal roots. Lancéreaux,[30] Westphal,[31] Friedländer,[32] and others may be cited as having found very distinct peripheral lesions in lead-poisoning. Whether these lesions begin in the nerve or in the muscles cannot be considered as determined. Birdsall[33] reported a case of what he believed to be a plumbic myositis, and Gourbault[34] describes primary alteration in the nerves, similar to those seen after section, as occurring in poisoned guinea-pigs, while Debove and Reaut[35] describe the first changes as resembling those of subacute myositis, and Friedländer emphatically asserts that lessening in the size of the muscular fibres and multiplication of the muscular nuclei precede the nerve-degeneration. On the other hand, Vulpian,[36] Monakow,[37] Oeller,[38] and a number of other observers* have noticed structural changes (poliomyelitis, capillary hemorrhages, etc.) in the spinal cord of men dead of plumbism; while Popow[39] found that when guinea-pigs were rapidly poisoned (six to eight days) with lead there was produced a central myelitis, which first affected the large cells of the gray matter, and afterwards involved the white matter, the peripheral nerve-filaments remaining normal. There is, however, no real contradiction, as Popow believes, between his observations and those of Gourbault,[40] for the latter poisoned his animals very slowly (six months), and it is not improbable that the rapidity of the poisoning had an influence upon the seat of the lesion. As already stated, the symptoms of plumbism may exactly simulate those of general poliomyelitis, and both Dégérine and Leopold Stieglitz[41] found degeneration of the motor cells. Karl Schaffer[42] believes that two sharply separated forms of degeneration of the nerve-centres occur in chronic lead-poisoning,—one consisting of a minutely granular destruction of the protoplasm, the other of the homogenization of the contents of the cell.

The evidence at present indicates that lead is capable of producing a peripheral neuritis, and also a centric poliomyelitis, which may or may not coexist in an individual case; the probabilities being in favor of a peculiar peripheral neuritis, as the primary lesion of ordinary plumbic wrist-drop (see paper by Schultze,[43] also Prevost and Binet). Hemorrhages into the nerve-centres sometimes occur.[44] There seems to be no doubt that lead really affects the nutrition of almost all of the higher tissues. In saturnine encephalopathy changes have been found in the ganglionic cells as well as in the neuroglia, with stenosis of capillaries and general shrinkage of the cortex (see O'Carroll[45]). Marked alterations are not rare in the kidneys and other glandular organs, and general

* For references, see *Arch. f. Psychiat. und Nervenkr.*, xvi. 477.

fibrosis of the blood-vessels is probably more or less developed in every slowly fatal case of chronic poisoning (case, Fisher[46]).

The *excretion* of lead with the gall is very active, but it is probable that it chiefly escapes from the body with the urine. The elimination seems to be capricious, and much affected by potassium iodide and by other influences.*

The treatment of chronic lead-poisoning evidently arranges itself under three indications: first, to prevent the ingestion of more of the poison; second, to aid in the elimination of that in the system; third, to relieve symptoms and restore lost functions. In lead colic the last two indications are met by purgatives, to which opium should be added to relieve pain. It is often necessary to use the most powerful drastics, such as croton oil; but senna, salts, and other of the milder cathartics should always be tried first. *Alum*, it is asserted, acts in some unknown way as a specific in lead colic, and from twenty to sixty grains of it may be given four or five times a day; but our experience is not favorable to its use. In the more chronic forms of lead-poisoning, to fulfil the second indication baths of potassium sulphuret should be employed, and potassium iodide be administered internally.† As the result of special investigation, Oddo and Silbert[51] conclude that the elimination of lead through the skin in chronic lead-poisoning is important, that it is facilitated by injections of pilocarpine, and that the sulphur baths are valuable in the treatment of chronic lead-poisoning. The bath should be given (A. Eulenburg[52]) in a wooden tub, two or three times a week, and should contain six or seven ounces of the salt. The patient, during the half-hour of his continuance in it, from time to time should be well rubbed with a coarse towel. On coming out he is to be thoroughly washed with warm soapsuds. The dose of the iodide should be from fifteen to twenty grains, administered after meals, in dilute solution. A case is reported[53] in which galvanic baths were used successfully, the patient being placed in the bath and the positive pole of a twenty-eight-cell battery applied to the nape of the neck, the negative to the feet. When severe cerebral symptoms arise, treatment is of little avail, and should be largely expectant.‡ In cases of lead-poisoning in which the symptoms resemble

* See Melsens,[47] Pouchet,[48] Annuschat,[49] and Pouchet.[50]

† As the result of a careful series of analyses, J. D. Mann (*Brit. Med. Journ.*, 1893, i.) concludes that in chronic lead-poisoning there is a great fluctuation in the elimination of lead, that potassium iodide has no real effect in increasing the elimination, that lead is eliminated from the intestines even more freely than from the urine, and that the previous contrary results obtained by investigators have been due to chance coincidences of the iodide treatment with increase of the lead excretions from other cause. He recommends especially *general massage*, and confirms to some extent the assertion of Tedeschi, that this massage increases remarkably lead elimination.

‡ It seems doubtful whether the sulphur baths really aid elimination, but we have certainly seen good follow their use. It has been denied that the iodide acts; but cases are reported in which lead was not in the urine before, and was after the administration of the drug (see *Brit. Med. Journ.*, 1880, ii. 1034). Moreover, John Marshall (*Therap. Gaz.*, iv. 97) has shown by actual experiment that potassium iodide in solution has an action on the insoluble lead carbonate and phosphate, with the formation of a soluble lead com-

those of acute poliomyelitis we have used ascending doses of strychnine with most extraordinary results, rapidly deepening paralysis being almost at once controlled. It is essential that the strychnine be pushed to the point of systemic intolerance. It is best to administer it by the mouth, or if used hypodermically it should be given at least twice a day. It may possibly prove of value in other acute forms of lead palsy.

The local use of electricity is exceedingly important to restore the lost function of nerve and muscle. When the faradic current elicits a response, it should always be employed ; but in some cases[54] the continued current retains its power after the induced has lost all its influence. The rule is always to apply that current which causes contraction ; if both fail, the continued current should be used, the poles being reversed at intervals of four or five seconds. The electrical séances should be triweekly, each lasting about fifteen minutes, and they should be persevered in for months. We have seen great improvement in a case which for the first four months yielded no results ; indeed, long after voluntary movement had in great measure returned, no form of electricity would cause contraction of the affected muscles.*

PHYSIOLOGICAL ACTION.—The symptoms of acute lead-poisoning are chiefly due to its local irritant action, but those of chronic poisoning are of wider significance. How the lead is absorbed to produce them is uncertain,—probably as an albuminate. All the compounds of lead and albumin as yet discovered by the chemist are, however, precipitated by alkaline carbonates, and cannot, therefore, exist in the blood.

The symptoms of chronic lead-poisoning are probably in great part secondary to the structural alteration produced by the drug, lead being a poison to all forms of protoplasm. Why in one case one set of organs should be attacked and in another case a different portion of the body is a mystery. The nephritis which is so common a result is no doubt connected with the effort to eliminate the poison from the system.

The chief research we know upon the effects of lead upon the lower animals is that of Ernest Harnack,[55] who employed the compound of lead and ethyl first discovered by Loewig. When this is injected into animals in large quantities it causes a rapidly fatal train of symptoms evidently due to the action of the compound

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pound,—double lead and potassium iodide; and therefore, if lead taken into the system be deposited in the tissues as insoluble carbonate or phosphate, these latter compounds, on the administration of potassium iodide, will be decomposed, with the production of a soluble lead compound, and consequently a more rapid elimination of the lead will occur.

* M. Semmola (*Bull. Acad. de Méd.*, 1892, xxviii.) asserts that chronic plumbism can readily be cured by the elimination of the metal from the urine under the influence of a constant galvanic current. He applies the positive pole upon the tongue and the negative pole over the region of the kidneys for a while ; later, places the positive pole upon the sides of the vertebral column and the negative pole upon the abdomen, keeping up the application for five to twenty minutes each day, using a current from one hundred to one hundred and fifty milliampères. He affirms that in cases in which no lead could be found in the urine, after three or four days of treatment the lead could readily be detected and that its quantity gradually increased.

itself. When, however, the introduction into the system has been slow, a chronic poisoning is produced by the lead set free in the blood and tissues.

Under these circumstances a constant symptom in both dogs and rabbits is diarrhœa, due to a violently increased peristalsis, with, in the dog, occasional attacks of colic. Harnack found that in dogs the lead ethyl produces violent excitement, with chorea, convulsions, etc., evidently due to an exciting or irritant action upon the cerebrum, and believes that this explains the saturnine cerebral cases sometimes seen in man.

The chief symptom of the poisoning in frogs was a progressive palsy of muscular origin. The muscle became exhausted on repeated galvanization much more rapidly than is normal, and after death was incapable of undergoing complete post-mortem rigidity. The peripheral nerves appeared to have escaped entirely. The heart-muscle shared the fate of the voluntary muscles. The muscular action of the poison was excessively pronounced in rabbits, but was feeble in dogs and cats. Different results have, however, been arrived at by H. von Wyss,[56] who found that the loss of reflex activity, etc., in the frog was not prevented by tying an artery so as to protect the leg from the poison, and that the protected muscle lost its power of responding to electrical stimulation just as fast as did the one reached by the lead. He concludes, therefore, that the paralysis is of centric origin. Curci[57] is stated to have proved that lead exerts an irritant influence upon the peripheral branches and ganglionic centres of the pneumogastric. According to the researches of Ellenberger and Hofmeister, in the sheep toxic doses of lead greatly depress the elimination of urea.

The pulse in lead colic is usually very hard and tense. Sphygmographic studies made of it by August Frank[58] and Ernest Bardenhewer[59] have been thought to indicate a condition of general arterial spasm, and have given rise to the theory that the colic is caused by intestinal anæmia from vaso-motor contraction. Harnack, however, found that in dogs and rabbits the lead ethyl has no action upon the vaso-motor system and does not produce spasm of the vessels. Moreover, he determined that both the diarrhœa and excessive peristalsis produced in dogs were arrested by atropine, which ought to promote rather than lessen vaso-motor contraction. Lead colic in man is probably due to a spasmodic contraction of the intestines so powerful as to arrest peristalsis, and to so press upon the blood-vessels as to force the blood from the abdomen into the general circulation.*

The following preparations of lead are official in the United States Pharmacopœia :

PLUMBI OXIDUM—LEAD OXIDE. U. S.

Litharge, which is prepared by blowing air through melted lead, occurs in small yellowish or orange-colored scales, which are insoluble in water and alcohol, but are soluble in acetic or dilute nitric acid and in a warm solution of the fixed alkalies. It is occasionally used as a desiccant astringent powder for ulcers, but its chief employment in medicine is in the making of EMPLASTRUM PLUMBI, or *Lead Plaster*, U. S., which consists chiefly of lead oleomargarate. Lead plaster occurs in

* Bardenhewer affirms that pilocarpine given hypodermically will relieve simultaneously the pulse and the colic.

grayish, cylindrical rolls, which become adhesive at the temperature of the body, and, spread upon kid, is sometimes used as a protective to parts exposed to pressure, or to superficial ulcers or abrasions. EMPLASTRUM RESINÆ, or *Resin Plaster*, U. S., or *adhesive* or *sticking plaster*, is made by incorporating resin with lead plaster, and, spread upon linen, is much used in surgery for mechanical purposes. EMPLASTRUM SAPONIS, or *Soap Plaster*, U. S., is made by the addition of soap to lead plaster. It is employed chiefly as a protective.

PLUMBI ACETAS—LEAD ACETATE. U. S.

Sugar of lead occurs in transparent, acicular, often aggregated, crystals, of a sweet, styptic taste. It is soluble in water, to which it usually imparts a slight milkiness. From its solution it is precipitated black by sulphuretted hydrogen, white by soluble carbonates, chlorides, and sulphates, and bright yellow by potassium iodide. It is also incompatible with the mucilage of slippery elm, but scarcely so with that of flaxseed or of pith of sassafras.

THERAPEUTICS.—A solution of lead acetate is used very largely in acute external *inflammations* as a sedative and astringent lotion. Although chemically incompatible, it is frequently combined very advantageously in these cases with opium. As a too concentrated solution acts as an irritant, the strength for use on the skin should not exceed ten grains to the ounce. In diseases of the eye it is condemned by oculists, because when there is any abrasion of the cornea it is very prone to deposit an opaque film.

Internally, lead acetate has been employed very largely in *hemorrhage;* indeed, George B. Wood[60] commends it as the most valuable of all astringents in *hæmoptysis*. We think it is now, however, rarely given for this purpose. Its chief use at present is in *diarrhœa*. On account of its sedative properties, when the purging is attended by inflammation it is the most serviceable of all the astringents; and, owing to the promptness of its action, it is also very valuable in cases with profuse serous discharges. Dose, two to five grains (0.13–0.32 Gm.), in pill, repeated *pro re nata*.

LIQUOR PLUMBI SUBACETATIS. U. S.—The *Solution of Lead Subacetate*, or *Goulard's Extract*, as it is sometimes called, is a colorless limpid liquid, of a sweetish, astringent taste. When exposed to the air, it rapidly absorbs carbonic acid and deposits lead carbonate, the neutral acetate being left in solution. In its action upon the human organism, Goulard's extract resembles very closely the simple lead acetate; but it is never used internally. Externally, it is a favorite application in cases of *sprains* or *bruises*, as well as in *superficial inflammation*. For this purpose it requires dilution, and from a fluidounce to four fluidounces of it may be added to a pint of water. When used upon a raw surface, the strength should not be so great. The *Diluted Solution* (LIQUOR

PLUMBI SUBACETATIS DILUTUS, U. S., strength three per cent.) is too weak to be of value.

PLUMBI CARBONAS, U. S., or *Lead Carbonate*, is a heavy, white, tasteless powder, insoluble in distilled water, but slightly soluble in water containing carbonic acid. It is used solely as an external sedative application. Rubbed up with linseed oil, it constitutes white lead paint, and in this form, or in that of the ointment (UNGUENTUM PLUMBI CARBONATIS, U. S.), it is a most efficient dressing for fresh *burns*. Care must be taken in its use, however, when a large surface is involved, as lead colic has been caused by its absorption.

PLUMBI NITRAS, U. S., or *Lead Nitrate*, occurs in white, nearly opaque, octahedral, very heavy crystals, soluble in two parts of water at 59° F., and in 0.75 part of boiling water; almost insoluble in alcohol. It is used chiefly as a disinfectant. Dissolved in water, it forms *Ledoyen's Disinfectant Solution*. It acts by decomposing the sulphuretted hydrogen, itself being converted into a lead sulphide. It is said to attack actively the soldering of pipes.[61] Lead nitrate is frequently used in *onychia maligna*. The dead part of the nail should be cut away, and the powdered nitrate thickly sprinkled over the surface; after a few days the slough separates, leaving a clean surface, upon which the new nail usually soon forms. Sometimes more than one application of the remedy is required.

BISMUTHUM—BISMUTH.

The metal bismuth is never used in medicine in its simple or metallic form. The insoluble official preparations are: BISMUTHI SUBCARBONAS —BISMUTH SUBCARBONATE, U. S., a white or yellowish-white powder, tasteless and odorless, totally insoluble in water, soluble with effervescence in dilute nitric acid; and BISMUTHI SUBNITRAS, or BISMUTH SUBNITRATE, U. S., a heavy white powder, odorless, with a faint acid taste, and a decidedly acid reaction when applied to moistened litmus-paper, almost insoluble in water, soluble without effervescence in nitric acid. The complicated official processes for the making of salts were designed to get rid of the arsenic, which contaminates all the bismuth ores of Europe. Of late years the South American bismuth has been introduced into commerce, and, as it contains no arsenic, commercial bismuth preparations are now pure.

PHYSIOLOGICAL ACTION.—The actions of bismuth subcarbonate and subnitrate are so exactly similar that they can practically be considered as one. Orfila and others of the older observers attributed to bismuth violent irritant properties, reporting severe symptoms and even death after its ingestion. These results were, however, due not to the bismuth, but to the arsenic with which it was contaminated. The soluble preparations of bismuth are, it is true, active irritant poisons (see BISMUTHI CITRAS), but the insoluble subcarbonate and subnitrate, when pure, have

practically no irritant influence. It was formerly denied that they are dissolved at all in the alimentary canal, but it is now certain that they are very slowly absorbed and as slowly eliminated. Harnack[1] affirms that the metal has been found by Orfila in the liver, spleen, and urine, and by Lewald in the milk. Bergeret and Mayençon[2] state that when bismuth subnitrate is administered the metal can always be detected, after a few hours, in the urine. They have also discovered it in the serous exudation of dropsy, and have proved that when a few grains of the salt mentioned are given to rabbits, in from twenty to thirty minutes it can be found in the urine, kidneys, spleen, blood, and muscles, and even eight days after the administration can be detected in all the tissues. Five days after the exhibition of a gramme of the subnitrate to a man they found traces of the metal in the liver and kidneys; but the analysis of the body of a woman dead sixty-two days after the ingestion of two grammes yielded negative results. E. S. Wood[3] also has detected bismuth in the urine four weeks after its last exhibition.

The discovery by Theodore Kocher[4] that the most insoluble bismuth preparations are actively antiseptic led to their use in surgery, and to the further discovery that when applied in very large quantities to extensive wounded surfaces they are capable of yielding so much bismuth to absorption as to produce a poisoning, which is characterized by acute stomatitis, sometimes gangrenous, with a peculiar black discoloration of the mucous membrane, usually beginning upon the borders of the teeth, but spreading over the whole mouth, followed by an intestinal catarrh with pain and diarrhœa, and in severe cases with desquamative nephritis, as shown by albuminous urine and epithelial tube-casts.*

That bismuth is capable of acting as a poison in the lower animals has been abundantly proved by the experiments of F. Balzer[5] and of P. Dalché and E. Villejean,[6] which show that, whether given by the mouth or hypodermically, repeated large doses of it produce gradual failure of strength, a peculiar stomatitis, and evidences of gastro-intestinal irritation, with death from exhaustion. Balzer states that the stomatitis which it causes differs from the stomatitis of ptyalism in the tendency to rapid gangrenous change; and also that the bismuth is eliminated with the saliva, bile, and urine, but has a distinct tendency to accumulate in the tissues.

THERAPEUTICS.—When brought in contact with the mucous membranes, the insoluble preparations of bismuth, by virtue of their weight, tend to adhere and to act as protectives; they also exert an antiseptic influence, and by their slow absorption produce a persistent—peculiarly persistent—sedative, astringent action. They are, therefore, of great service in the treatment of irritations and inflammations of those mucous membranes with which they can be brought in contact. Thus, they are useful to allay *vomiting* dependent upon gastric irritation. In simple neuralgic *gastric pain* following eating, especially when occurring in feeble, badly nourished subjects, bismuth is often of great service; and even in *carcinoma* it may palliate by alleviating pain and vomiting. In

* For cases, see Kocher, also Petersen (*Deutsches Med. Wochenschr.*, June 20, 1883).

pyrosis it is sometimes successful ; in gastric and enteric catarrhs it is a standard remedy. In the simple *diarrhœa* of irritation and in the *chronic diarrhœa* of camps the bismuth preparations are often very efficient; and in the chronic *bowel complaints* of children, especially as seen in the summer season, given with pepsin, they are almost invaluable. Bismuth is a very valuable topical remedy in the treatment of mucous inflammations and of ulcers to which it can be applied directly. Thus, in the beginning of a *gonorrhœa*, the injection every two hours of a mixture containing twenty grains of bismuth to the ounce usually brings immediate relief ; in a similar way it may be employed in *leucorrhœa* and in *acute coryza*. In Germany it has been to some extent used as a surgical dressing.

ADMINISTRATION.—In order to get the best attainable results from the use of bismuth subnitrate it is necessary to vary the dose and method of administration. In stomachic affections from five to fifteen grains may be given preferably when the stomach is empty, in order that the bismuth may be distributed as closely as possible over the gastric mucous membrane. In intestinal diseases from fifteen grains to a drachm (1–4 Gm.) may be exhibited in capsule from one to two hours after meals at a time when the gastric contents are escaping through the pylorus. Children bear proportionately very large doses : thus, five to ten grains may be given to a two-year-old infant.

BISMUTHI CITRAS. U. S.—The insoluble *bismuth citrate* is not used in medicine, but has been introduced into the Pharmacopœia for the production of the soluble BISMUTHI ET AMMONII CITRAS, U. S. We know of no recorded cases of poisoning by this salt, which, however, is undoubtedly capable of acting as a powerful corrosive poison.

According to Feder-Meyer[7] the *Bismuth and Ammonium Citrate* causes in rabbits violent tremblings with diarrhœa, accompanied after large doses by disturbance of the sensibility and of coördination, tetanic cramps, altered respiration (in the beginning accelerated and superficial, afterwards becoming slow), continual lowering of the blood-pressure, and death. The same observer noticed in chronic poisoning similar symptoms with albuminous urine and after death fatty degeneration of the liver, heart, and renal secreting structure. Similar observations were made by Mory,[8] who states that the death in mammals is the result of cardiac paralysis, and that in the advanced stages of chronic poisoning, when the blood-pressure is very low, it is not elevated by stimulation of the splanchnic nerves nor by asphyxia. W. Steinfeld[9] has obtained in the frog from the administration of bismuth ammonio-citrate and ammonio-tartrate peculiar tremblings of the voluntary muscles with prolongation of contraction upon stimulation with the galvanic current, and slowing of the heart's beat, also after sufficient doses paralysis of nerves and muscles; effects which he attributes not to the bismuth, but to the acids of the preparations. He states that the proper symptoms produced by the metal appear only after some hours, and consist of motor excitement with reflex cries which are due to irritation of the medulla oblongata. In acutely poisoned mammals he noticed vomiting and purging, convulsions with loss of power, slowing of the pulse, and sinking of the blood-pressure, believed by him to be all of centric origin. In chronic poisoning

there was loss of certainty of movement with cardiac depression followed by increasing paralysis, usually ending in death without convulsions. In his studies upon absorption and elimination he found that the ammonio-citrates and ammonio-tartrates are quickly eliminated through the kidneys, so that, as a rule, after from ten to fifteen hours they can no longer be found in the blood, tissues, or urine.

THERAPEUTICS.—The ammonio-citrate of bismuth in small dose is actively stimulant, astringent, and, probably, germicidal. In large dose it is a violent irritant. It has none of the peculiar properties which grow out of the insolubility of the subnitrate, but is more astringent, and has been used in *chronic diarrhœa* and in the *acute diarrhœas of relaxation.* Dose, two to five grains (0.13–0.32 Gm.) in dilute watery solution, repeated every three to six hours *pro re nata.*

Besides the preparations of bismuth recognized by the U. S. Pharmacopœia, the activity of the pharmacists has thrown into the market a large number of combinations of the metal, some of which have been used to a considerable extent, but no one of which has ever been the subject of a complete scientific investigation. The most important of these compounds is probably *Bismuth Subgallate*, a dry, yellowish-saffron, odorless powder, which, under the proprietary name of *Dermatol*, has been employed as a local antiseptic in *wounds*, *chronic eczema*, and other surgical affections, and in doses of from seven to thirty grains (0.5–2 Gm.) internally in *diarrhœas.* It has been shown both by Bluhn and by Colasanti that its germicidal influence is very slight, certainly not superior to that of the official salts of bismuth, and we can see no reason for supposing that it has any superiority in internal diseases.

The *Bismuth Salicylate* recognized by the British Pharmacopœia is a white amorphous powder, insoluble in water, containing sixty-two to sixty-four per cent. of bismuthic oxide. It has been much used internally, possibly under the belief that it is slowly decomposed in the intestines with the elimination of salicylic acid, a belief which is founded on speculation and not on knowledge. We have never been able to perceive any difference in its action from that of the official salts of bismuth. Dose, ten to twenty grains (0.65–1.3 Gm.).

The *Bismuth Oxyiodide*, a light yellowish-red crystalline powder, is sometimes used as a local remedy, especially as a substitute for iodoform and in *gastric ulcer.* Dose, five to ten grains (0.32–0.65 Gm.).

CERII OXALAS. U.S.

Cerium oxalate is a white powder, insoluble in water, alcohol, and ether, but soluble in sulphuric acid. It has been employed in medicine quite largely for the relief of *vomiting*, especially when dependent upon *pregnancy* or other forms of *uterine disturbance.* Its action on the economy has not yet been made out, but it may be tried with some hope of success in cases of nervous or dyspeptic vomiting. The dose is one to three grains (0.06–0.19 Gm.), in pill, three or four times a day.

ZINCUM—ZINC.

ZINCI SULPHAS—*Zinc Sulphate.* U. S.—*White Vitriol* occurs in irregular white masses, the *pure* zinc sulphate in minute, transparent, four-sided, prismatic crystals, which effloresce slightly in dry air, and are soluble in 0.6 part of water at 59° F., and in 0.2 part of boiling water, also soluble in about three parts of glycerin ; insoluble in alcohol. The taste is styptic and peculiar.

THERAPEUTICS.—Zinc sulphate is in weak solution a stimulant astringent, in concentrated form an active irritant. Emetic dose, thirty grains (2 Gm.). In doses of one grain (0.06 Gm.), it has been given in pills as a stimulant astringent in *chronic diarrhœa* with ulceration.

TOXICOLOGY.—Zinc sulphate in large doses acts as an irritant poison, producing violent vomiting, colicky pains, diarrhœa, prostration, etc. The symptoms which it causes are almost identical with those produced by the corresponding salt of copper. Alkalies and their carbonates are the chemical antidotes to it, producing insoluble precipitates. Eggs and milk should also be exhibited, and the symptoms treated as they arise. Chronic zinc-poisoning, if it really exists at all, is very rare, and the metal seems to be used with impunity in cooking-utensils.

Schlockow[1] affirms that zinc-smelters rarely live to be over forty-five years of age, dying sometimes of catarrh of the bronchial or alimentary mucous membranes, or, in other cases, of a peculiar nervous affection, which commences with burning superficial pains, exalted sensibility, and reflex activity in the legs, and afterwards puts on still more clearly the features of myelitis ; and A. Sacher[2] finds that intravenous injection of very large doses of zinc salts produces paralysis of the voluntary muscles.

ZINCI OXIDUM VENALE.—*Commercial zinc oxide* is a snow-white powder, obtained by burning the metal in the air. It should be used only in pharmacy. The pure oxide (ZINCI OXIDUM, U. S.) is a yellowish-white powder, insoluble in water, but soluble without effervescence in dilute acids.

THERAPEUTICS.—Zinc oxide is used externally as a mildly astringent, slightly stimulant, and desiccant application in *skin diseases* and to *ulcers*. When given continuously in small doses it is believed to act as a tonic and alterative upon the nervous system. It has also been commended as an astringent in chronic *catarrhal diarrhœa* of adults and infants, and has been largely used in *epilepsy* and in *chorea*. Dose, one-half to two grains (0.03–0.12 Gm.). The ointment (UNGUENTUM ZINCI OXIDI, U. S.,—one part to four of benzoinated lard) is useful in various *skin diseases*.

ZINCI CARBONAS PRÆCIPITATUS. U. S.—*Precipitated zinc carbonate* is intended to replace the old impure native carbonate, *calamine*. It is made by precipitating the zinc sulphate by the sodium carbonate. It is a white powder, closely resembling in its medical properties zinc oxide.

ZINCI ACETAS. U. S.—*Zinc acetate* is made by the action of acetic acid upon the commercial zinc oxide. It occurs in white, micaceous crystals, which effloresce in a dry atmosphere and are very soluble in water. The taste is astringent and metallic. The zinc acetate resembles in its physiological and therapeutic qualities the sulphate, but is probably somewhat less active. It is chiefly used in collyria (one to two grains to one fluidounce), and as an injection (one to twenty grains to one fluidounce) in *gonorrhœa*.

CADMIUM is employed in medicine to some slight extent in the form of its *sulphate*, which is stated to resemble closely zinc sulphate in its therapeutic properties. It has been especially used as an astringent stimulant in collyria, made by dissolving half a grain to four grains in an ounce of rose-water. Strangely enough, some physicians who have employed it state that it has ten times the strength of the zinc salt, others that it is about equivalent to it.

CUPRUM—COPPER.

CUPRI SULPHAS—COPPER SULPHATE. U. S.

Copper sulphate occurs in blue, transparent, slightly efflorescent, rhomboidal prisms, or their fragments. It dissolves, at 59° F., in about 2.6 parts of water and in 0.5 part of boiling water; almost insoluble in alcohol. With ammonia its solution precipitates a bluish-white cupric hydrate, which redissolves when an excess of the alkali is added, forming a rich deep blue solution.

PHYSIOLOGICAL ACTION.—In very dilute solution the copper sulphate acts locally as a stimulant and mild astringent; in a more concentrated form it is an irritant; in powder it is a very mild caustic, which is scarcely capable of destroying sound tissue. The salts of copper in sufficient amount are poisonous to all forms of protoplasm. Coupin[1] found that 0.0055 per cent. solution of soluble salt of copper will prevent germination of wheat: that copper compounds affect violently the general nutrition in animals is shown by the production of fatty degeneration by them (see Ellenberger and Hofmeister). According to Falck,[2] the cupric sulphate causes in the lower animals great depression of temperature, with progressive general paresis, ending in death, apparently from failure of respiration. When the copper salt was given hypodermically, vomiting was not produced; although when it was exhibited by the mouth, emesis was very violent and persistent.

THERAPEUTICS.—Internally the small dose—one-quarter of a grain (0.016 Gm.) in pill form—of cupric sulphate is occasionally administered in chronic *enteritis* and *colitis* with *ulceration*. Formerly copper salts were employed in various nervous affections, but they are of no service. The old belief that when taken in small continuous doses cupric sulphate had a strengthening effect upon the nervous system has no apparent foundation.

The chief value of the so-called *blue stone* is as an external application. When applied in solid form to ulcers, it destroys flabby granulations and exerts a powerful excitant influence. Its solution acts more feebly, and is sometimes employed as a dressing for indolent *ulcers*, but more frequently as a stimulant and alterant to mucous membranes, as in *granular conjunctivitis*.

Toxicology.—The symptoms of acute copper-poisoning generally come on in about a quarter of an hour, but may be postponed for from one to two hours. They consist of violent vomiting and purging, accompanied by very severe colicky pains. The matters vomited are greenish or bluish, the stools glairy, mucous, and at times bloody. There is a very strong taste of copper in the mouth, and often constant expectoration ; excessive salivation and bronchial secretion are stated by Galippe[3] to be characteristic. Death may occur in a few hours, preceded by convulsions, paralysis, delirium, anæsthesia, and other symptoms of great nervous disturbance, seemingly as the result of a direct action of the poison upon the nervous system. Sometimes a tendency to syncope is very marked, and as both L. Schwarz[4] and W. Filehne[5] have found that toxic doses of copper salts paralyze the heart in the lower animals, cardiac death probably occurs in human poisoning. The urine is usually lessened or suppressed. Black urine, due to the presence of hæmoglobin without unaltered blood-corpuscles, has been noted ; in this case, after death all the tissues were found stained with altered blood, and evidently destruction of the blood was an important factor in the fatal result ;[6] fatty degeneration of the liver was also found. If the patient survives for twenty-four hours, jaundice nearly always shows itself. After this, profound depression with nervous symptoms may develop and end in death ; but not rarely a favorable issue results, in which case the symptoms of gastro-intestinal inflammation with fever develop themselves. The copper is said to be eliminated more freely with the salivary and intestinal secretions than with the urine (Galippe).

As the action of the cupric sulphate is exceedingly rapid, any antidote to be of avail must be given at once and act quickly. In the poisoning milk, eggs, or other albuminous substance should be exhibited immediately, freely, and repeatedly.* Soap or a fixed alkali may be used. The yellow *prussiate of potash*, when pure, is harmless, and precipitates instantly an insoluble compound of copper from solutions of its salt. When it is to be had in time, it may therefore be used as an antidote to the sulphate. The treatment of copper-poisoning after the administration of the antidote consists in meeting the indications as they arise ; opium should be used freely. When death occurs, the results of gastro-intestinal inflammation are usually found ; sometimes the intestine has a decided bluish tint, and occasionally submucous ecchymoses occur. In

* No time should be lost in attempting to separate the yolk from the white of the egg, but the egg should be broken into a bowl as quickly as possible, a little water added, and the whole stirred up and exhibited.

exceptional cases, it is said, there are no evidences of inflammation in the alimentary canal.* Fatty degeneration of the liver has been noted in man.[6]

If chronic copper-poisoning ever exist among workers in the metal, it must be very rarely. The chief symptoms are asserted to be "a coppery taste in the mouth, giddiness, pain in the bowels, vomiting, occasional diarrhœa, and wasting of the body." Clapton [7] has pointed out, as characteristic, a *green* line upon the gums ; this has also been observed by Taylor, but its constancy is not assured. Thus, a green line was found on the teeth of all but two or three of a number of workers in the metal examined by a committee of the London Clinical Society,[8] but there was no line on the gums of any of them.

When copper is given to the lower animals in continuous sufficient dose it produces loss of appetite, failure of digestion, diarrhœa, and other evidences of gastro-intestinal catarrh ; with marked evidences of disturbances of the nutrition, such as emaciation, failure of the heart, and with a progressive paralysis and failing respiration ending in death. After death alterations of the blood and wide-spread fatty degeneration have been noted by numerous observers.† According to Von Bókay,[9] the muscles are very early affected, cloudiness of their protoplasm and disappearance of their cross-striation coming on. The liver and kidneys, however, are especially attacked : in the beginning there are hyperplasia of the connective tissue and subacute nephritis, followed by fatty degeneration and finally atrophy.

Although Galippe and Burcy and also Ducom [10] affirm that copper is almost without influence upon dogs, and Galippe [11] fed himself for one month on food containing a large amount of copper without causing any symptoms of intoxication, it is certain that whilst very minute quantities of copper may be taken internally habitually without producing injury, larger doses may slowly and insidiously work out fatal consequences. The matter is important because the metal is habitually used in the canning of vegetables, French peas, beans, etc., owing their attractive color to their treatment with copper, which can be chemically recognized in them.

The possibility of injury from such food has been repeatedly investigated by French and Belgian commissions, and the general verdict has been that no harm is produced. The fact that twenty millions of cans of these food-articles are consumed every year, and that after thirty-six years' continuance of the custom it has

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*For a fatal case of repeated poisoning by copper, with much information of value to chemical experts, see *La France Méd.*, September, 1874, abstracted in *Half-Yearly Compendium*, January, 1875. Bournevette and Yvon (*Revue Scientifique*, 1874, 859) found two hundred and ninety-five milligrammes of metallic copper in the liver of a woman who had taken the ammoniacal sulphate three months previously. Minute quantities of copper exist in the normal human body (*Bull. Thérap.*, xciii. 88).

† Falck (*Deutsch. Klinik*, 1859, xi.), Ellenberger and Von Hofmeister (*Arch. Wissen. Prakt. Thierheilk.*, x. 228), W. Filehne (*Deutsch. Med. Wochen.*, 1893, xxi.), De Moor, Von Bókay (*Pester Med.-Chir. Presse*, 1897, 33), Baum and Seeliger (*Archiv f. Thierheilk.*, 1897, xxiii., 1898, xxiv.), and Trolldenier (*Archiv f. Thierheilk.*, 1897, xxiii.).

not been clearly established that harm is done, indicates that in the amount used the vegetables containing copper are not poisonous. It is plain that the freedom from injury depends upon the minuteness of the amount of copper ingested; the Italian law does not allow more than 0.05 gramme of copper per kilo of food, but the researches of Tschirch would indicate that a food containing this amount of copper, if very freely taken, might do harm.*

ARGENTUM—SILVER.

ARGENTI NITRAS—SILVER NITRATE. U.S.

This is a heavy anhydrous salt, crystallizing in translucent, shining, rhombic plates, and having a styptic, metallic, corrosive taste. It is soluble, at 59° F., in 0.6 part of water, in twenty-six parts of alcohol, in 0.1 part of boiling water, and in five parts of boiling alcohol. For external use the crystals are melted and run into moulds, where they harden into round, grayish, brittle sticks, about the size of a goose-quill, and having a radiated crystalline fracture. These constitute the official ARGENTI NITRAS FUSUS. As only the pure salt will make well-formed crystals, the impure products are always manufactured into the fused nitrate, which should therefore not be employed internally. When silver nitrate, either in substance or in solution, is exposed to the conjoint influence of light and of even a minute portion of organic matter, it turns black, and is converted into an insoluble substance, which has been believed to be metallic silver, but is more probably an oxide. For this reason the white stains which it first makes when applied to living tissues soon blacken.

PHYSIOLOGICAL ACTION.—*Local Action.*—Silver nitrate coagulates albumin, and, when applied in its pure state to living tissues, acts as a caustic, coating them over with a white almost membranous film. The caustic action is, however, not a deep one, because penetration of the salt into the tissues is soon prevented by the thick and tough skin or stratum which is formed. When applied in a dilute solution it acts as an astringent, constringing the vessels and overcoming relaxation. Its local action, however, is not simply that of an astringent, but is certainly peculiar and apparently alterative to nutrition. It is also a very active germicide.

Absorption and Elimination.—It is evident that in the stomach silver nitrate cannot long maintain its integrity. Bogolowsky[1] has found that when the nitrate is added to a peptone it is readily dissolved, and that the solution formed does not coagulate albumin.† That in this or in some other analogous form silver is absorbed is proved by its having been found in various internal organs and by the discoloration which follows its protracted use: *argyria* of authors. When it is exhibited for a long continuous period, the skin often acquires a peculiar bluish slate color, which may become very dark, and in decided cases the

* For discussion upon the subject, see De Moor (*Archives de Pharmacodynamie*, 1895, i.) and Tschirch (*Toxicologie und Hygiene*, Stuttgart, 1893).

† For recent studies of this character, see Isidore Neumann (*loc. cit.*), also A. von Fragstein (*Berlin. Klin. Wochen.*, 1877, 294).

conjunctiva and even the mucous membrane of the mouth are involved. The silver is found in all the tissues of the skin below the rete Malpighii* (Frommann,[2] Riemer,[3] Neumann[4]). E. Harnack[5] asserts that in all recorded cases of argyria at least thirty grammes of the salt have been taken. The staining of the skin is always preceded by a dark discoloration of the mucous membrane of the mouth and gums. Both Heller and Orfila failed to detect silver in the urine of animals taking it; but probably it is eliminated, though slowly and in very small quantities, by the kidneys.

General Effects.—As silver is never given for an immediate therapeutic action, its acute physiological action is of less interest to the therapeutist than to the toxicologist, and the detailed symptoms of its poisoning are considered under the head of toxicology. In general these symptoms consist of those of gastro-enteritis with violent disturbance of the nervous system, due to a direct action of the poison upon the cerebrum and the spinal cord.† Although the circulation is profoundly affected, death appears to take place from centric paralysis of respiration.

By an elaborate series of experiments Charles Rouget[6] has shown that upon all animals from a crab to a dog the soluble salts of silver act as a poison, causing in mammals vomiting and purging, and in them and the lower animals violent disturbance of the motor functions, as shown by paralysis and convulsions, and of the respiration, ending finally in death by asphyxia. This is in accord with the observations of other investigators. Rabuteau and Mourier affirm that the almost instantaneous death which Charcot and Ball first noted as following the injection of a large dose of silver nitrate into the veins is due to a direct paralyzing influence of the drug upon the muscle of the heart. Rouget has never seen this form of death follow the hypodermic or internal administration of the poison, the heart always continuing to beat for a greater or less length of time after the cessation of respiration, and also retaining its irritability.

As already stated, both convulsions and paralysis are present in acute silver-poisoning. The convulsions are severe, generally tetanic, and according to Rouget are plainly reflex. A peculiarity noted by Rouget is the persistence of the convulsions after the complete abolition of voluntary movements. Curci[7] affirms that they are due to excitation of the motor tract of the cord, and that this is preceded by a similar influence upon the sensory tracts.

The death is due, in argyria, to cessation of the respiration; Rouget even states that he has witnessed the suspension of the latter function in the frog while the

* In an elaborate study of the organs of a case of argyria, Riemer detected the silver in the glomerules of the kidney, the intima of the aorta, the choroid plexus, and the mesenteric glands. He believes that it is never deposited inside the cells, and that the silver preparation is reduced in the intestines, and the fine particles of the silver carried in the blood and lymph. Gerschun (*Arbeiten aus Physiolog. Inst. zu Dorpat*, x.) coincides with Riemer in affirming that the silver is deposited outside of the cells, but O. Loew (*Pflüger's Archiv*, xxxiv. 603) asserts that it occurs inside of the renal endothelial cells. Jahn (*Beiträge z. Patholog. Anat.*, xvi.) states that the unstriated muscular fibres and the elastic tissue have a special power of reducing silver.

† Orfila and other of the earlier observers experimented upon it by injecting it directly into the veins of animals. When exhibited in this way, it must, by coagulating the albumin of the blood, produce thrombi, to which the subsequent symptoms are in greater or less measure to be ascribed. This method of experimentation can, therefore, throw but little light upon the action of silver nitrate when taken into the stomach.

blood was also rendered very aplastic, as was betrayed by the constant tendency to the formation of ecchymoses. As some one has suggested that the silver in these cases replaces the iron of the blood-corpuscles, Bogolowsky made a chemical examination of the latter, but failed to find any traces of silver in them,—no doubt because it was not there. The solid tissues were found, after death from chronic argyria, to be in an advanced stage of degeneration, which especially affected epithelial structures. The first change was swelling and opacity of the cells, with obscuration of the nucleus. After this came fatty degeneration, fatty globules in the cell, destruction of nucleus, and finally of the cell itself. The liver and kidneys were profoundly influenced, as was also the muscular structure, especially of the heart. These results obtained by Bogolowsky have been in the main corroborated by A. V. Rózsahegzi.[9]

THERAPEUTICS.—The results of the chronic poisoning by silver are in every way so closely analogous to those produced by antimony, arsenic, copper, and other metallic poisons as to show that silver belongs to that class of drugs which in some way markedly affects the general nutrition. It cannot, however, be called an alterative, as at present we know of no application of its power to the needs of practical medicine.

The only advantageous use of silver in therapeutics is for its local action either upon the surface of the body or upon those mucous membranes that can be reached directly by the drug.

As a simple *caustic*, the salt may be used whenever a superficial action only is required: for reasons already given (page 406), it is useless whenever it is necessary to produce a deep eschar. As a *caustic alterative*, it is applied in solid form to many *ulcerated surfaces*, for the purpose of destroying superficial diseased tissue and of substituting, when the eschar separates, a healthy for an unhealthy action. As an *antiphlogistic*, silver nitrate acts not only as an astringent, but also as a germicide. In the various inflammations of the mucous membranes, such as *conjunctivitis*, *faucitis*, *laryngitis*, *urethritis*, etc., it is used very frequently, not only in the stage of relaxation, but also in the beginning of the attack. In *conjunctivitis*, the solution employed should not, under ordinary circumstances, be stronger than one or two grains to the ounce; and it should not be used at all if any corneal ulceration exists, since a deposit of silver is liable to occur and to produce opacity. In *faucitis*, the strength of the solution may vary from thirty to sixty grains to the fluidounce. In ordinary cases of *sore throat*, the application once a day or every alternate day is generally sufficient. It is best made by means of a good-sized camel's-hair brush, each part of the inflamed surface being distinctly touched, and not the whole simply daubed or slopped over by means of a very large brush or a sponge probang. In severe cases it may be necessary to use the solution twice a day. Even a saturated solution can scarcely be looked upon as caustic to the more robust mucous membranes.

Carl Seiler[10] states that while solutions of silver nitrate of less than sixty grains to the ounce cause pain when applied to the throat, solutions of one hundred and twenty to two hundred and fifty grains act as local anæsthetics, relieving soreness,

and usually arresting acute inflammations at once, if applied in the first twenty-four hours, before inflammatory exudation has occurred.

In *laryngitis*, the solution may contain from ten to twenty grains to the ounce, and should be applied with a brush by the aid of the laryngoscopic mirror. An attack of *urethritis* may sometimes be aborted in its forming stage by the injection of a strong solution (twelve grains to one fluidounce) of the salt ; but the practice is of doubtful expediency, since when it fails it greatly aggravates the trouble. When *chronic gonorrhœa* is strictly localized to a small spot in the posterior urethra, installation of from five to ten minims of a solution of the strength of five to ten grains to the fluidounce is often serviceable. When the inflammation is more diffused, irrigation with a weaker solution is preferable ; at first 1 to 5000 may be employed, and the strength gradually increased to even 1 to 500.

Freely applied to the skin of the whole finger, silver nitrate will sometimes abort a commencing *felon*, or, applied to the scrotum, an *epididymitis*.

Internally, silver nitrate is exceedingly useful in stomachic and to a less extent in enteric diseases, exerting no doubt a purely local influence. In that form of *dyspepsia* characterized by the vomiting of large quantities of yeasty fluid, it has yielded in our hands better results than any other remedy ; and the same may be said of *chronic gastritis* and of *gastric ulcer*. The rules of administration are identical in these three diseases. In the first place, regulation of the diet is imperative : if the case be a bad one, all eating of meals should be suspended, and the patient receive every two or three hours a cup of sweet milk, with sound toasted bread broken up and thoroughly softened in it. In order to wash off as much as possible the mucous membrane of the stomach, and to neutralize the acids of the stomach, forty-five minutes before the meal fifteen to twenty grains of sodium bicarbonate should be exhibited in a tumblerful of hot water, and ten minutes later a quarter of a grain of silver nitrate should be given in pill form. The use of cold water at meals should be absolutely forbidden, and in very serious cases, when all food is rejected by the stomach, it is sometimes advisable to allow absolute rest for two or three days to that viscus, the patient being fed by the rectum, and only a little water and pills of silver with opium being taken by the mouth. Under these circumstances, the return to the usual method of taking food must be very gradual, at first only a tablespoonful each of milk and of lime-water being administered every hour. In *chronic enteritis* or *colitis*, silver nitrate is sometimes of service, especially if there be ulceration.

For its constitutional effects silver nitrate is used solely in diseases of the nervous system. It was formerly given in *epilepsy*, but it has passed out of use. In *chronic inflammations* of the spinal cord, whether affecting chiefly the posterior columns and constituting *locomotor ataxia*, or the

anterior and giving rise to *paraplegia*, it is still employed, but is of doubtful value.

Toxicology.—The symptoms produced by the ingestion of large doses of silver nitrate are partly gastro-intestinal and partly cerebro-spinal. In some instances the one series of phenomena predominate, in others those of the other class. In a case[11] at the Hôpital St.-Louis in 1839 the symptoms were insensibility, violent convulsions, dilated pupils, and, when consciousness was partially regained, intense gastric pain: complete restoration of consciousness did not occur until eleven hours after admission, and the coma returned at intervals during several days.

Vertigo, coma, convulsions, great muscular weakness, and paralysis, with intense disturbance of respiration, are in these cases the manifestations of disturbed innervation, whilst the abdominal symptoms are those of gastro-enteritis. The diagnosis can generally be made by the discolorations of the lips and skin—at first white, afterwards black—and by the blackish or brownish vomit; when the customary antidote has been given, both vomit and stools are generally white and curdy. After death the stomach and bowels are found corroded, often ecchymosed and with patches of a white or grayish color. Poisoning by silver nitrate is not common, and we know of but three fatal cases,—one in 1837 (Taylor[12]), one in 1861, a woman killed by fifty grains in solution in divided doses, and one in 1871, a child destroyed by a piece of the solid stick three-quarters of an inch long, in spite of the use of the antidote (Scattergood[13]).

The treatment consists in the administration at once of large amounts of *common salt*, alkaline carbonates, or soap,—the chemical antidotes,—the constant use of large draughts of milk, and the meeting of symptoms as they arise.

The fatal dose of silver varies very much, according, no doubt, to the presence of substances capable of decomposing it in the stomach. Thirty grains have killed, and recovery has taken place after the ingestion of an ounce (case, Husemann[14]).

Chronic *argyria*, or discoloration of the skin by silver, is usually unaccompanied by disturbances of health, although in severe cases the discoloration affects not only the skin, lips, gums, and sclerotic, but even the internal organs, such as the liver, spleen, and kidneys. It is therefore not due, as has been thought, to the silver chloride, since the latter becomes dark only under the influence of the light, but to a deposition of silver itself or of its oxide.*

S. Krysinski[15] found the granules in almost every tissue of the body, and states that they are an organic compound of silver, the exact nature of which has not yet

* According to Rózsahegzi, Hermann has seen one case in which preceding the deposition of the silver there were malaise, emaciation, failure of memory, singing in the ears, deafness, and spasms of the ocular muscles.

been determined. The minute quantity of the metal present is shown by the analysis of Versmanns,[16] who in 14.1 grammes of dried liver found only 0.0068 gramme of metallic silver (0.047 per cent.), and in 8.6 grammes of dried kidney 0.053 gramme (0.61 per cent.). Greater or less success has been asserted for various treatments in argyria, but in general they are equally futile.

Rogers states that blistering will lighten the color very much, and Eichmann asserts (Husemann) that he has cured two cases by the use of potash baths and of soap baths, each four times a week. The older authorities commend the use of potassium iodide internally. L. P. Yandell[17] has reported two cases in which large doses of the iodide were given for many months for syphilis, and the mercurial vapor-baths used at the same time for the same purpose, with the result of a complete cure of the argyria. The fading was gradual.

ADMINISTRATION.—The silver nitrate should always be given in pill, and, when it is desired to obtain its constitutional influence, after meals, during the process of digestion; but when its local action on the stomach is required, it should be administered one or two hours before meals; and if the intestines are to be reached, the pill should be enclosed in two thick capsules. The administration of silver nitrate should not extend over a longer time than two months without a protracted intermission. The dose is one-quarter of a grain (0.016 Gm.).

ARGENTI NITRAS DILUTUS, U. S., is a grayish, solid substance, often in crayons, composed of two parts of potassium nitrate with one part of silver nitrate. It may be used as a very mild caustic.

Silver oxide (ARGENTI OXIDUM, U. S.) is an olive-brown powder, very slightly soluble in water, which may be prepared by precipitating the silver nitrate with solution of potassa. It was introduced into medicine as a substitute for the nitrate, with the idea that it would accomplish in diseases of the nervous system all that that drug is capable of, and at the same time not discolor the skin. With our present knowledge of the method of absorption of the nitrate, this seems highly improbable, and it is contradicted by experience.[18] Silver oxide is not caustic when locally applied, but probably exerts some astringent action, and it has been commended in *pyrosis*. In nervous affections it is probably of equal value with the nitrate. The dose is a grain (0.06 Gm.), in pill, three or four times a day.

Silver cyanide (ARGENTI CYANIDUM, U. S.) is used solely for the preparation of hydrocyanic acid. *Silver iodide* (ARGENTI IODIDUM, U. S.) has been used as an alterative, but is of very doubtful value.

ARGENTUM SOLUBILE.—*Soluble Silver.—Colloidal Silver.*—In 1889 M. Carey Lea[19] described several allotropic forms of silver, among which was a lilac or greenish-blue variety, freely soluble in water, yielding a bright red solution. Its use in practical medicine was first suggested by Credé[20] on the supposition that it would be a non-toxic, soluble antiseptic, for which purpose it has been used by several clinicians in doses of thirty to forty-five grains (2–3 Gm.), or by inunction as preferred by

Credé, ten grammes of the fifteen per cent. ointment being rubbed in vigorously for a quarter of an hour. The one per cent. solution may be injected hypodermically without causing pain. There has not been, however, any scientific investigation of soluble silver, and the clinical studies have not been sufficient to establish its value.

ARGONIN.—*Argentum Casein.*—A substance prepared by mixing a solution of sodium compound of casein with silver nitrate, and precipitating with alcohol. It is readily soluble in warm or albuminous water, and has been highly recommended by numerous German and American clinicians as a local application in *gonorrhœa;* its ten per cent. solution is said to produce no pain in acute cases and may be used freely.

ARGENTI CITRICUM.—*Itrol.—Silver citrate* has been used to some extent in *gonorrhœa* in a solution of 1 to 4000. It is asserted to be intensely poisonous to the gonococcus and non-irritant to the urethral mucous membrane.

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FAMILY II.—TONICS.

MINERAL TONICS.

FERRUM—IRON. U.S.

SINCE iron constitutes a necessary integrant portion of the red blood-corpuscles, it is a food rather than a medicine. A large proportion of the various articles of ordinary diet contain a trace of it, and it must undoubtedly find entrance with the food into the blood. Although a great amount of work has been done by chemists upon the absorption and elimination of iron, the results have been so imperfect, contradictory, and difficult of explanation that they are at present of very little use to the clinician. Iron is probably at all times in the urine in minute quantities. Among the older chemists, Quevenne taught that the exhibition of the salts of iron had little influence upon the amount of iron in the urine, whilst Becquerel found that the increased elimination of iron commenced directly after the first taking of a ferruginous preparation, and, though varying notably from day to day, continued on the whole until the end. Among the later chemists, Bunge, of Basel, believes that no salts of iron are absorbed into the blood, and that the value of the iron in chlorosis is due to its local action on the gastric juices. His theory is that in chlorosis there is a great poverty of gastric juice, with an excessive formation of alkaline sulphides ; that these alkaline sulphides decompose the absorbable albuminous iron compounds of the food, and render them, like ordinary salts, incapable of absorption ; and that the ordinary iron preparations occupy the alkaline sulphides, and allow the albuminous iron compounds to be absorbed.

Bunge bases his theory upon the experimental results obtained by himself and by Hamburger,[1] which he believes prove, first, that in the healthy subject the continued administration of iron does not raise the red blood-corpuscles or hæmoglobin ; second, that when iron is given it does not increase the amount excreted in the urine. The researches quoted later in this article (page 416) throw, however, the gravest doubt upon the theory of Bunge. Moreover, it is directly opposed by the research of Carl Th. Moerner,[2] who finds as the result of the study of urinary indican, etc., during the administration of iron, no reason for believing that the salts of iron act as intestinal antiseptics.

The researches of certain Dorpat investigators and of Peter Robert Berry, epitomized below, would also appear to prove that the Pharmaco-

pœial preparations of iron, when taken into the organization, are not absorbed,—a conclusion, however, which, for reasons given a little later, cannot be accepted.

Nicolai Damaskin, Johann Kumberg, Chr. Busch, and Eugen Stender, working with and under the immediate supervision of Kobert, of Dorpat, found, *first*, that the presence of iron can be demonstrated in normal filtered or unfiltered urine, both quantitatively and qualitatively; that the elimination of iron does not cease, as has been affirmed, during fasting in man; and that the administration of an official preparation of iron does not cause iron to disappear from the urine: *second*, that the iron exists in the urine in two portions, one in the morphological elements, normal and pathological, of the urine, the other dissolved in the urine itself; it being doubtful whether the iron is or is not simply in the coloring-matter of the urine, but it being certain that this iron in solution is in some very permanent combination, as it resists even heating of the urine with muriatic and nitric acids: *third*, that the normal relation of the iron in the morphological elements to that in solution appears to be from one to seven to one to eight: *fourth*, that the daily elimination of iron in the urine is scarcely one milligramme, but is subject to much variation, according to nourishment, etc.; in sickness attended by destruction of the blood, or with increase of the morphological elements of the urine, the elimination of the iron increases, but the presence of biliary coloring-matter in the urine has no influence upon it: *fifth*, that when iron and sodium citrate is injected subcutaneously into man, in the dose of one milligramme per seven kilogrammes of weight, forty per cent. of the iron escapes in the urine unaltered, such injections being, however, attended by distinct danger of renal irritation, so that hypodermic injections of iron should be given in very minute doses only: *sixth*, that the administration of the ferrous citrate or of the saccharated iron carbonate by the mouth, in doses of one hundred milligrammes a day, or the rubbing into the skin of the same preparations, does not perceptibly alter the elimination of iron; so that positive proof is still wanting that this and similar preparations of the Pharmacopœia are taken up by the human organism, although Kunkel reached opposite results upon animals. In Busch's experiments it was found that either pure or impure hæmoglobin, given internally, moderately increased the elimination of iron from the urine. Peter Robert Berry[3] in a micro-chemical study failed to detect in the intestinal walls of the animal the iron which had been exhibited shortly before.

Notwithstanding all the laboratory evidence just summarized, every clinician knows that almost any one of the ordinary preparations of iron is capable of increasing the amount of iron in the blood in chlorosis, and until some plausible reason other than that which is natural—namely, that the iron acts after absorption—is given, it remains highly improbable that iron is unabsorbed. The conclusion that the *human body is capable of absorbing iron* from the Pharmacopœial preparations has, moreover, recently received so much of experimental corroboration that it would appear to be an established truth.

In the *first* place, Socin[4] has shown that it is scarcely possible to determine the question of iron absorption by the simple comparison of the iron ingested and eliminated. In the *second* place, the chemists upon whose work so much has been presaged studied the renal elimination of iron only; whereas the metal escapes even more freely through the intestinal tract than through the kidneys. Thus, Gottlieb, feeding dogs on food practically free from iron, was able to obtain from the

fæces nearly ninety-seven per cent. of iron which had been subcutaneously injected. He also demonstrated that twenty to sixty-five per cent. of the injected iron could at a certain time be found in the liver. Carl Jacobi[5] found that after the intravenous injection of iron, renal elimination ceased in the dog in from two to three hours, after which fifty per cent. of the injected iron could be recovered from the liver. Zaleski[6] affirms that iron is especially eliminated by the liver.

In the *third* place, there is direct proof of absorption. Kunkel[7] for eight weeks fed two dogs upon milk, giving to one of them iron in addition, and bleeding each dog equally from time to time. After the killing of the dogs the blood and the various organs of the body were carefully analyzed, and it was found that iron was in distinct excess in all the organs of the dog to which the metal had been given, and that in the blood there was one and a half times as much of the iron, and in the liver eight times as much, as in the similar tissues or organs of the dog used for control. Justus Gaule[8] detected chemically iron in the lymph coming from the thoracic duct of a rabbit into whose stomach a dilute solution of the ferric chloride had been injected. Quincke[9] not only proved that iron is excreted from the mucous membrane of the large intestine, but also that absorbed iron can be detected in the walls of the duodenum, a fact which has been confirmed by Hall,[10] by A. Hoffmann,[11] and by Hare.[12] Hall further discovered that if the feeding of a carnivorous animal with iron had been long continued, the metal could be detected in the pulp-cells of the spleen and in the hepatic acini around the central vein. The conclusion of Hall, that iron occurs in the human system in two forms, one a fixed organic combination,—hæmoglobin,—the other an inorganic or a very loose organic combination, is very plausible. According to Hall, it is the second combination whose amount in the system continually varies with that of the iron taken into the alimentary canal.

Spurred on by the theory that the inorganic preparations of iron are not absorbed, pharmaceutical chemists have put forth many organic preparations. Of these, *dried blood* or an *impure hæmoglobin* was naturally the first to be exploited. Bunge suggested a ferruginous nucleo-albumin obtained from egg-yolk, to which he gave the name of *hæmatogen;* whilst Schmiedeberg and Marfori,[13] under the name of *ferratin*, commended a proteid compound containing from four to eight per cent. of iron, which is affirmed to be the form in which iron exists in the liver, and out of which in the body the hæmoglobin is directly made. There is, however, neither clinical nor experimental evidence indicating that ferratin is superior to the older compounds. Hochhaus and Quincke[14] found that ferratin and the older compounds could be traced through the duodenum into the mesenteric glands with equal facility; and in an elaborate study on the absorption and elimination of the iron, Cloetta[15] was unable to perceive any difference between organic and inorganic preparations of iron in relation to their building up of the blood.

When, in anæmia, there is need of more supply of material for the manufacture of blood-corpuscles, the immediate usefulness of iron is very explicable; but in most cases of serious anæmia, as met with in disease, there seems to be no such need of ferruginous food; and it is a very important question, which at present, however, we cannot answer with any degree of positiveness, whether medicinal iron has or has not any stimulant influence upon those organs which produce the red blood-corpuscles.

passed off or is removable, and in which iron may be given as an aid to the rebuilding of the blood,—we find that practically the anæmias are divided into two sets: those in which there is a pronounced lessening in the percentage of hæmoglobin in the blood but not a corresponding lessening in the number of red blood-corpuscles, and those in which the red blood-corpuscles are greatly diminished in number. The first class of cases is typified in chlorosis, the second in the essential anæmias.

Of the value of iron in *chlorosis* there can be no doubt. Thus, Simon[19] reports a case of chlorosis in which, under the steady use of iron for sixty-four days, the globulin increased from 30.86 parts to 90.80 parts per thousand, and the hæmoglobin from 1.431 parts to 4.598 parts per thousand; and Cutler and Bradford[20] have obtained confirmatory results with Malassez's tubes. In most cases of *essential anæmia* with great lessening in the number of red blood-corpuscles, typified by *leukæmia* and *pernicious anæmia*, iron is of no service whatever. Unfortunately, the line between the two sets of cases of anæmia is in nature not so sharp as it can be made in treatises, and we have seen cases presenting a chlorotic form of anæmia, in which the anæmia failed to be affected at all by iron or any other treatment, remaining almost as persistent and unconquerable as the blood-lesion of leucocythæmia.

Almost all the preparations of iron are more or less astringent, and when in the blood very probably exert a direct influence upon the tissues, contracting them not merely by increasing their tone, but also by acting on their vital contractility.

The preparations of iron may be divided into those which are soluble and those which are insoluble in water. At first sight it would appear that the former class of preparations would be those most readily absorbed. The experiments of Quevenne have, however, demonstrated that solubility is, so far as iron is concerned, no evidence of absorbability. Quevenne asserts that the reduced iron yields the largest percentage to the gastric juice, and, as it is nearly free from astringency, it is one of the best of the chalybeates for use in pill form: but little, if any, inferior is the saccharated carbonate. If a soluble preparation be desired, the ammonic or potassic tartrates are very unirritating. When freely given, almost all preparations of iron form in the intestines sulphides, which blacken the fæces.

There are persons in whom iron produces headache: this can in some cases be obviated by the use of laxatives. The observations of M. Petit, N. A. Bubnow,[21] etc., that the iron preparations in large doses inhibit the digestive processes, throw some light upon these cases. Our experience is that gouty or rheumatic patients bear iron badly, and that sometimes its exhibition seems to aggravate the arthritic symptoms. The chief contra-indications for the use of iron is the existence of *plethora* or of catarrhal disease of the gastro-intestinal tract.

The peculiar actions of certain salts of iron will be considered under their respective preparations.

(MISTURA FERRI COMPOSITA, U. S.) contains the ferrous carbonate and myrrh, and has been much used in *anæmia* with *amenorrhœa* in doses of from one to two tablespoonfuls (15–30 C.c.).

FERRI SULPHAS—FERROUS SULPHATE. U. S.—*Ferrous sulphate* occurs in transparent, efflorescent, rhombic prisms of a pale bluish-green color and a metallic styptic taste. It is a very decided astringent, and in a concentrated form and sufficient amount acts as an irritant poison, producing vomiting, purging, and gastro-intestinal inflammation.* Externally its solution (five to twenty-five grains to the fluidounce) has been used as an astringent lotion, especially in *erysipelas*. As a simple chalybeate the ferrous sulphate should never be used. In *chronic diarrhœa* it is sometimes employed as a tonic astringent. Dose, one to two grains (0.06–0.12 Gm.); in the form of the dried sulphate (FERRI SULPHAS EXSICCATUS, U. S.), one-half to one grain (0.03–0.06 Gm.).

LIQUOR FERRI SUBSULPHATIS—SOLUTION OF FERRIC SUBSULPHATE. U. S.—MONSEL'S SOLUTION.—The *solution of the subsulphate* (of the sesquioxide) *of iron* (often incorrectly called *solution of the persulphate of iron*) is a very active astringent and blood-coagulant: being also only slightly irritant, it is perhaps the most efficient of the styptics, but must in *hemorrhage*, to be efficient, be applied directly to the part. In *hæmatemesis* five minims (0.3 C.c.) of it may be given in from one to two ounces of water, repeated if necessary. The atomization of its watery solution (from five to twenty drops to the ounce) often acts well in *hæmoptysis*. The pulverization of the liquid should be complete, and the inhalation, which should last for five to twenty minutes, may be repeated at intervals of an hour or longer. In *diphtheria* Monsel's solution is very valuable applied freely, of full strength or diluted *pro re nata*, to the throat every three to twelve hours. In overdose Monsel's solution is an irritant poison; the antidote is soap or an alkaline carbonate.

The *Solution of Ferric Sulphate* (LIQUOR FERRI TERSULPHATIS, U. S.), owing to its irritant action, is used only to make the ferric preparations.

TINCTURA FERRI CHLORIDI.—*Tincture of Ferric Chloride*, twenty-five per cent., U. S., contains the ferric chloride, hydrochloric acid, and alcohol, and, from the reactions of the last two ingredients, chloric ether. It is a reddish-yellow liquid, actively chalybeate, very astringent, and possessed of peculiar properties, some of which may be due to the ether in it. Decidedly diuretic and escaping through the kidneys, it directly affects the genito-urinary mucous membrane. It is much used in *chronic Bright's disease* and combined with tincture of

* In a case reported in the *N. Y. Med. Journ.*, xxxviii. 401, the early symptoms, as stated by the patient, were chiefly nervous: little confidence can, however, be reposed in the patient's report of symptoms or of the amount ingested.

cantharides in *gleet*. In *erysipelas* it is constantly employed with remar able results, controlling the disease in a manner not yet understoo Analogy has suggested its employment in other adynamic affectio such as *diphtheria* and *pyæmia*, but its value in these diseases is mu more doubtful. It is so destructive to the teeth that except in the too less its use as a gargle is unjustifiable; and even in its ordinary the peutic use, by the employment of a tube, etc., the teeth should be p tected as far as possible. Dose, ten to thirty drops (0.6–2 C.c.) as chalybeate three times a day, in *erysipelas* every two or three hou The orange-yellow, crystalline, deliquescent *Ferric Chloride* (FER CHLORIDUM, U. S.) is rarely used.

SYRUPUS FERRI IODIDI. U. S.—The *Syrup of Ferrous Iodide* is transparent, greenish liquid, of a sweet, ferruginous taste. It depos no sediment on keeping, and should not affect the color of starch. I strikes a blue color with the latter substance, it contains free iodine. T syrup of ferrous iodide is a favorite remedy in those cases of anæmia which there is a distinct scrofulous taint. It is believed to possess peculiar alterative powers of iodine, conjoined with the tonic proper of iron. It is much used in *scrofulosis* occurring in anæmic childre but it certainly possesses no advantages over a ferruginous tonic a iodine when given separately but simultaneously. Dose, for a child t years old, five to ten drops (0.3–0.6 C.c.); for an adult, thirty to fo minims (2–2.5 C.c.). As it affects the teeth very seriously, it sho always be freely diluted when taken, and the mouth should be w washed after its administration.

FERRI IODIDUM SACCHARATUM. U. S.—*Saccharated Ferrous Iod* is a yellowish-white or grayish powder which represents the chemical a medical properties of the corresponding syrup, being prepared by parallel process. It may be substituted for the syrup in doses of fr two to five grains (0.13–0.3 Gm.), given in pill form.

FERRUM DIALYSATUM.—*Dialyzed Iron* is a clear, neutral, nea tasteless, dark red liquid, prepared by dialyzing a solution of the ch ride of iron. Its exact chemical composition is uncertain, but it is unstable that a precipitate is at once produced by minute quantities alkalies, almost all soluble salts, and many organic substances. Owing its tastelessness and its freedom from astringency it was for a short ti much used as a chalybeate in doses of from twenty to forty drops (1. 2.5 C.c.), but the ferric oxide which results from its immediate precipi tion in the stomach is a very feeble substance, and the preparation l almost passed out of vogue. It may, however, be used as an antid to arsenic. Doses of a tablespoonful (15 C.c.) may be given every f or ten minutes *pro re nata*.*

* See *Phila. Med. Times*, viii. 104, 151, 335.

There are five official *Iron Citrates*, each soluble in water. Two of these (FERRI CITRAS and FERRI ET AMMONII CITRAS) occur in garnety scales, and are simply mild chalybeates. Dose, five grains (0.3 Gm.). The *Iron and Quinine Citrate* (FERRI ET QUININÆ CITRAS), in transparent scales, varying from reddish brown to yellowish brown in color, and *Soluble Iron and Quinine Citrate* (FERRI ET QUININÆ CITRAS SOLUBILIS, U. S.), each containing twelve per cent. of alkaloid, may be given in doses of five grains (0.3 Gm.) or more. The *Iron and Strychnine Citrate* (FERRI ET STRYCHNINÆ CITRAS) contains one per cent. of strychnine.*

There are two official *Iron Tartrates* (FERRI ET AMMONII TARTRAS and FERRI ET POTASSII TARTRAS), each occurring in garnety scales, and each soluble in water. Dose, five grains (0.3 Gm.). The *Ferrous Lactate* (FERRI LACTAS, U. S.) occurs in greenish-white crystalline crusts or grains, soluble in forty parts of water. It is a good chalybeate. Dose, five grains (0.3 Gm.). *Soluble Ferric Phosphate* (FERRI PHOSPHAS SOLUBILIS) and *Soluble Ferric Pyrophosphate* (FERRI PYROPHOSPHAS SOLUBILIS) are excellent preparations, occurring in apple-green scales, completely soluble in water, and nearly free from astringency and ferruginous taste. Dose, five grains (0.3 Gm.). *Ferric Ammonium Sulphate* (FERRI ET AMMONII SULPHAS, U. S.) occurs in octahedral crystals of a pale violet color: it is freely soluble in water, is very astringent, and is used only in atonic *leucorrhœa*, in which affection marked benefit is often gained by the exhibition of it in five-grain doses three times a day. *Iron Bromide* (not official) has recently been highly recommended by Da Costa[22] in *chorea* and *incontinence of urine* in children. He gives, to a child, five grains, dissolved in syrup, and rapidly increases the dose to twenty grains (0.3–1.3 Gm.). In a few trials we have found it useless in *chorea*.

MANGANESE.—The *Manganese Dioxide* (MANGANI DIOXIDUM, U. S.) and the *Manganese Sulphate* (MANGANI SULPHAS, U. S.) have been supposed by some to possess therapeutic properties similar to those of iron. The metal manganese certainly exists in the blood, but its salts have failed to gain the confidence of the profession, although highly recommended by Harmon, of Belgium, and by Pétrequin[1] as an adjuvant to the chalybeates. In Garrod's[2] experiments upon anæmia the preparations of manganese failed to be of service. According to C. C. Gmelin, the sulphate acts as a powerful cholagogue on the lower animals, and Thomson states that it is a purgative to man in doses of one or two drachms. Leand[3] affirms that the manganese oxide is therapeutically equivalent to the preparations of bismuth excepting in that it does not constipate, and that it may be used with advantage in *gastralgia*, *py-*

* The alkaloidal compounds with iron are very ineligible preparations, because they do not allow the practitioner to vary the proportionate doses of the two ingredients.

rosis, and similar stomachic derangements. Dose, five to fifteen grains (0.3–1 Gm.)

MINERAL ACIDS.

Sulphuric, hydrochloric, nitric, and nitro-hydrochloric acids, when in concentrated form, rapidly destroy all organic tissues, and are, therefore, corrosives, hydrochloric acid being the feeblest.

Owing to its abstraction of the element of water from the carbon of organic tissues, sulphuric acid blackens organic matter at the same time that it destroys its texture ; nitric acid stains organic tissue a deep yellow color ; nitro-hydrochloric acid produces a somewhat similar but much less pronounced discoloration. In the detection of poisoning by one of these agents the color of the stain upon the person or clothing is often of great assistance. Holes made in the linen by one of these acids are to be distinguished from those made by fire or mechanical violence by the pulpy character and acid reaction of the edges.

The general symptoms of poisoning by mineral acids are similar, and depend for their severity especially upon the amount and the concentration of the dose taken, although sulphuric and nitric acids are more powerful than is hydrochloric acid.* Death from collapse has resulted in two and a half hours, but months may be required in the working out of the fatal result. The symptoms are immediate pain in the mouth, gullet, and epigastrium, violent vomiting (after sulphuric acid the matters may be tarry), and rapid collapse marked by cold wet surface, feeble pulse, and suppressed voice. The mind is usually clear until very late in the poisoning.

After a small dose the chief symptoms may be connected with the upper digestive passages. Thus, Maukopff has recorded suppurative parotitis largely due to the closure of the duct of Steno. Ulceration of the larynx or œsophagus has frequently been noted. Desquamative nephritis may be developed several days after subsidence of the first symptoms. In a case of sulphuric acid poisoning recorded by Maukopff, the urine which had ceased to be albuminous on the third day became so again on the twentieth, with a simultaneous development of casts containing blood-corpuscles ; after death tubular nephritis was found. Another symptom noted by Maukopff was intercostal neuralgia.

After death, destruction of the œsophagus, stomach, or air-passages is usually found, the color of the slough—black after sulphuric, yellow after nitric acid—being characteristic. Probably in all cases in which death does not take place too early, wide-spread degeneration of protoplasm takes place. A. D. Kazowsky,[1] has found that this involves the cells of the heart-ganglia, which undergo parenchymatous swelling, followed by necrosis of the cells and vacuolization not only of the nuclei but also of the general protoplasm.

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* Cases of sulphuric acid poisoning (*Med. Times and Gaz.*, 1863, i.).

When the dose has not been sufficient to kill, protracted illness from local organic alterations usually results.

The treatment of a case of acid-poisoning consists in the immediate administration of soap, chalk, whitewash, magnesia, or other available antidote. Notwithstanding Christison's condemnation of the alkaline carbonates as too irritating, they should be used unhesitatingly in dilute form if immediately at hand.

ACIDUM SULPHURICUM. U. S.—SULPHURIC ACID.—*Oil of Vitriol* is, when pure, a colorless, heavy liquid which on exposure to the air rapidly absorbs moisture.

Concentrated sulphuric acid is not rarely used as an escharotic, for which purpose it is mixed with finely powdered charcoal so as to form a paste. Appropriately diluted, it has been employed as a stimulant and astringent lotion in *venereal* and other indolent *ulcers*. Internally, sulphuric acid is very useful as an astringent in *colliquative sweats* (*night-sweats*) and in profuse *serous diarrhœas*. We have used it with great advantage in the sudden serous vomiting and purging of infants known as *cholera infantum*.

It has been employed with advantage in *cholera*, and a remarkable series of observations by R. G. Curtin[2] at least furnish good reason for further testing its powers as a prophylactic against this disease.

The facts recorded by Curtin are as follows. A very severe epidemic of the disease ceased in the Insane Department of the Philadelphia Almshouse within twelve hours after the lunatics were all put upon the free use of sulphuric acid lemonade, the only new case after this being in a man who refused to use the prophylactic. Two days after the use of the sulphuric acid was stopped two new cases occurred, and the epidemic was again arrested by the use of the acid. In the surgical wards of the Hospital Department the acid was used from the beginning of the epidemic; and these wards, although in no way isolated, were the only parts of the institution unvisited by the disease. The sulphuric acid probably acted by producing an excessive acidity of the alimentary canal, it being well assured that the cholera organism will develop only in an alkaline condition of the alimentary tract. Thus, the dog, whose digestive tract is highly acid, resists the action of the bacillus unless an alkaline carbonate be freely given, when choleraic symptoms appear after the administration of the cholera organism.

Sulphuric acid was formerly used in *hemorrhages*, but is now rarely employed. It is, we think, much less efficacious than are some other remedies. In *acute lead-poisoning* the dilute acid is an efficient antidote, and in white lead works the free use of sulphuric acid lemonade by the employees is said to be advantageous as a prophylactic against the chronic poisoning.

ADMINISTRATION.—Sulphuric acid should be given properly diluted, and with the requisite precautions to prevent its injuring the teeth. It is best administered in the form either of the dilute (ACIDUM SULPHURICUM DILUTUM—ten per cent. by weight, U. S.; sp. gr. 1.070; dose,

fifteen to thirty drops (1–2 C.c.) or of the aromatic sulphuric ac (ACIDUM SULPHURICUM AROMATICUM—about twenty per cent. weight, U. S.). The last preparation contains alcohol and aromatics. dose is from ten to twenty drops (0.6–1.3 C.c.), well diluted.

ACIDUM HYDROCHLORICUM. U. S.—*Hydrochloric Acid* is a col less aqueous solution of hydrochloric acid gas, having the specific grav of 1.163 and containing 31.9 per cent. by weight of the gas. The y lowish tint of commercial hydrochloric acid is due to the presence ferric chloride, organic matter, or other substance.

Hydrochloric acid, being the normal digestive acid of the stoma is often advantageous in cases in which chronic *indigestion* is connect with the failure to secrete acid in the stomach, and the combination it with strychnine, bitter tonics, and aromatics is often serviceable. the so-called "Swedish plan" of treatment of *typhoid fever*, hydrochlo or other mineral acid is given in very large quantities. Although t method was at one time much in vogue, it has no justification in resul and is to be avoided. The local use of hydrochloric acid in *diphther* made famous by Bretonneau, has deservedly gone into oblivion. A poison, hydrochloric acid is the most feeble of its class, recovery hav occurred after the ingestion of an ounce.*

ADMINISTRATION.—The acid is best given in the form of the offi ACIDUM HYDROCHLORICUM DILUTUM (ten per cent.; sp. gr. 1.05 Dose, ten to thirty drops (0.6–2 C.c.), properly diluted.

ACIDUM NITRICUM. U. S.—*Nitric Acid* is a liquid of the spec gravity of about 1.414, which as first made is colorless, but by expos to the light acquires a yellow tint. It oxidizes all the common met except gold, and is exceedingly corrosive to living tissue, which it sta an indelible yellow. When diluted it converts most animal and vege ble substances into oxalic, malic, or carbonic acid.

When taken internally in small amount, nitric acid acts as a stimul upon the glandular system of the alimentary canal, and in *serous di rhœa* appears to exert an astringent influence.

Nitric acid is frequently used as a powerful escharotic in cases *chancre*, *venereal* or other *warts*, *hospital* and other *acute gangrenes*. many instances in which formerly it was relied upon it has been replac by antiseptic measures.

In its employment care should be taken to protect the sound tissue by oil still better, by a layer of soap. It may be applied by means of a splinter of wo or, if it is to be used more freely, by a little mop. When it has penetrated as dee as is desirable, washing the part with warm soapsuds will prevent further action

Internally, nitric acid has been used in *low fevers*, but with very dou ful advantage. In *dyspepsia*, in *chronic hepatic congestion*, in the *oxa*

* See *Boston Medical and Surgical Journal*, xv.

acid diathesis, and in the *dyscrasia* of *constitutional syphilis* nitric acid has been employed with advantage, but is much inferior to nitro-hydrochloric acid.

In 1826 Hope asserted that ACIDUM NITROSUM has a specific action in *serous diarrhœa*, including the sudden acute diarrhœas of hot climates, and in the chronic *dysenteries* originating under similar circumstances. The formula he employed is as follows: ℞ Acidi nitrosi, fʒi; Misturæ camphoræ, fʒviii; Misce, et adde Tinct. opii, gtt. xl. S.—A fourth part to be taken every three or four hours.

Under the name of *Hope's Camphor Mixture* a preparation similar to this has been much used, but has gradually lost the confidence of the profession, chiefly, we believe, because on theoretical grounds the original formula has been departed from. The *Nitrous Acid* of the shops (ACIDUM NITROSUM, Edinburgh Pharmacopœia) is an orange-red liquid, which may be looked upon as a solution of nitric oxide in nitric acid. When it is diluted with water it is after a short time converted into simple nitric acid. For this reason it has been customary to substitute nitric acid for the Acidum Nitrosum of Hope's original formula. It should be noted, however, that the latter provided only sufficient of the remedy to last a few hours, and, as the reaction which has been spoken of requires some time for its performance, we do not think that theory in truth warrants the change. Practically we have failed with the new formula, when immediate relief was afterwards obtained by the use of the medicine prepared according to the old plan. Made in this way and used while fresh, Hope's Camphor Mixture is a very efficient though disagreeable remedy in *serous diarrhœas* connected with disordered secretion of the liver and other glands of the alimentary canal.

ADMINISTRATION.—The dose of the strong acid is from five to twenty drops (0.3–1.2 C.c.); of the diluted (ACIDUM NITRICUM DILUTUM—ten per cent. by weight, U. S.; sp. gr. 1.057), from fifteen to sixty drops (1–4 C.c.), well diluted.

ACIDUM NITRO-HYDROCHLORICUM. U. S.—*Nitro-Hydrochloric Acid* is made by mixing nine parts of nitric acid with forty-one parts of hydrochloric acid. If the acid be sufficiently strong, an orange-colored liquid will be formed with the evolution of intensely irritating vapors.

After standing for a length of time, the *red* color of freshly mixed nitro-hydrochloric acid changes to a golden yellow. It is in this state that the U. S. Pharmacopœia directs the acid to be used. By longer standing the *golden* yellow becomes *lemon* yellow, and the odor of chlorine is almost entirely lost. These changes are hastened by light, but will occur in the dark and in well-stopped bottles. Although the golden-yellow acid is directed by the Pharmacopœia, yet careful clinical studies have convinced us that the acid acts much more efficiently when freshly prepared and of a deep red color. In some cases it has seemed to us useful only when in the latter form. The lemon-yellow acid is comparatively inactive.

The remedial value of nitro-hydrochloric acid depends chiefly upon the power which it possesses to a much greater degree than any other of the mineral acids of influencing the action of the liver and other

glandular organs of the alimentary canal. Originally proposed by Scott, of Bombay, in the *chronic hepatitis* of hot climates, it has been used with great success by Annesley, Martin, and other famous India surgeons. The remedy would seem not to be indicated in hepatitis with high fever and a tendency to rapid suppuration so much as in the slower form of the affection, which normally ends in chronic enlargement and induration of the viscus. Both in the habitual *congestion* of the *liver* and in the milder affection known as *biliousness*, whose pathology is probably a torpid condition of the small glands of the alimentary mucous membrane as well as of the liver, nitro-hydrochloric acid has yielded in our hands most excellent results. That the remedy does act upon the liver is proved by the fact that in these cases it sometimes produces violent bilious diarrhœa. When *jaundice* depends upon obstruction or upon any of the severer organic diseases of the liver, the acid is of little if any use ; when, however, the jaundice depends upon torpor of the liver, or even when it is catarrhal in origin, the remedy may be of great service. Even in the early stages of *cirrhosis*, while the liver is still enlarged, nitro-hydrochloric acid should be tried, as in some cases apparently of this character great benefit has been derived from its use.

In those forms of *chronic diarrhœa* in which the disease is really an intestinal dyspepsia, nitro-hydrochloric acid may be of great service. As the effect of the acid is not a sudden one, it is evident that it acts in these cases not as an astringent, but by restoring the normal digestive power.

There is a morbid condition, *oxaluria*, probably dependent upon defective primary assimilation, in which the chief symptoms are general malaise, a feeling of weakness, a lack of elasticity, and a very great depression of spirits, with the crystals of calcium oxalate generally present in the urine, and in which nitro-hydrochloric acid produces in a few days a surprising revolution.

As a "blood-purifier" the acid has been employed in *constitutional syphilis* and in various ulcerative *skin affections*. In these diseases it no doubt does good by improving digestion and increasing glandular action, but there is no reason to believe that it is a direct alterative.

ADMINISTRATION.—For reasons which have already been given, when nitro-hydrochloric acid is administered internally it should be freshly prepared ; and, as the changes which have been spoken of take place more rapidly when the acid is mixed with water, the official *dilute* nitro-hydrochloric acid is an ineligible preparation. As light hastens its deterioration, the strong acid should always be kept in a dark bottle with a glass stopper. Directly after mixing the acids the evolution of gas may be so great as to necessitate its being allowed to escape. After six or eight hours, however, the bottle should be closely stopped. The dose of the strong acid is from five to eight drops (0.3–0.5 C.c.), properly diluted, and taken through a tube after meals.

In *chronic hepatic diseases* the external application of the acid seems

to give even better results than its internal use. In India, according to Sir Ranald Martin, the bath is used as follows.

Take Hydrochloric acid f℥iii, Nitric acid f℥ii, Water f℥v. Mix. Two gallons of water and six fluidounces of the above mixture suffice for a bath, which will keep fit for use during three days, provided half a fluidounce of acid and a pint of water are added morning and evening. The bath must of course be given in wooden or earthenware vessels, and if it becomes necessary to warm it only a portion should be heated and the rest then added. In urgent cases the whole body may be immersed in the bath; but generally a foot-bath is preferable, the inside of the thighs and arms and the hepatic region being at the same time sponged. The bath should be repeated twice daily, lasting each time for ten or fifteen minutes.

We have had no experience in this method of using nitro-hydrochloric acid, but have derived great benefit from the application of the acid over the hepatic region.

A large piece (eight by ten inches) of spongio-piline, or of canton flannel (several layers), should be wrung out in a lotion of a strength varying, according to the irritability of the patient's skin, from one to three fluidrachms to the pint, and applied over the right hypochondrium, and covered with a piece of oiled silk supported by a bandage. The application sometimes causes a prickling sensation, and after a time may produce a profuse local sweating. The dressing may be left on from half an hour to an hour, and be repeated three or four times a day: some patients can wear it almost continuously.

Lactic Acid (Acidum Lacticum, U. S.).—W. Preyer,[3] conceiving that sleep is due to the presence in the blood of the results of tissue-change, among which is lactic acid, experimented with it and its soda salt, and announced that they acted as powerful soporifics upon both man and the lower animals. According to his statements, with the sleep came deep, slow respiration, and lessening of reflex activity and of the bodily temperature. It has, however, been shown * that the hypnotic powers of lactic acid and its salts are very feeble and uncertain. The large doses used also are very prone to produce irritation of the alimentary canal, and Senator noticed the production of rheumatic pains. From three to nine drachms (12–36 Gm.) of the sodium lactate may be given at a dose.

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MINERAL ACIDS

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FAMILY III.—ALTERATIVES.

THERE are employed by practitioners of medicine, to affect certain diseases most intimately connected with the processes of nutrition, various substances which do not, at least in the doses commonly used, produce any very obvious symptoms. It is to medicines of this character that the name of *Alteratives* has been applied, because when administered they seem simply to alter morbid processes.

Speculation has been rife as to the mode in which alteratives influence the body; and as the accepted pathology has been humoralistic or otherwise, so has it been strenuously argued that they act upon the vital fluid, or upon the solids of the body. The term "purifying of the blood" has been especially applied to their action, and is sufficiently suggestive of their function as viewed from the pathological stand-point of the old humoralist. What we know of the action of these medicines at present amounts to this, that they modify the nutritive processes of the body. To deny, as has been done, the existence or value of medicines of this class because we cannot tell why mercury relieves syphilis or why potassium iodide cures rheumatism is as absurd as to deny the existence of the syphilitic and the rheumatic dyscrasia because we do not know their ultimate nature.

PHOSPHORUS. U.S.

Phosphorus is a translucent, when pure nearly colorless, but usually slightly yellowish, highly inflammable elementary body, which is tasteless, but possessed of a peculiar alliaceous odor. It is insoluble in water, sparingly soluble in ether, absolute alcohol, and the oils, freely so in chloroform. It takes fire at 100° F., and melts at 111.2° F. In the shops it is in cylindrical sticks, covered with a whitish layer, and having when cut a waxy consistence and lustre. It occurs in several allotropic forms,—red phosphorus, black phosphorus, and the crystallized metallic phosphorus of Hittorf, whose physiological properties have not been investigated.

PHYSIOLOGICAL ACTION.—The physiological action of phosphorus in therapeutic doses is probably entirely different from that which it exerts when in larger amounts. It is a constituent of most of the more important tissues, and is especially abundant in the nerve-centres. Like iron, cod-liver oil, etc., when given in minute quantity it appears to act as a stimulant to the nutrition of the tissues, into whose composition it enters. So far as the nervous system is concerned, this assertion rests chiefly upon clinical observation; but Wegner[1] (confirmed by S. Miura and W. Stoeltzner[2]) has experimentally demonstrated such an action

upon the bony tissues. When adult animals are fed upon minute doses of phosphorus the spongy tissue in the long and short bones becomes thickened and the compact tissue more dense. After a time new tissue is deposited upon the inside of the shafts of the long bones, in some instances until the marrow-cavity is obliterated. The action upon the bones of growing animals is even more marked.

Phosphorus was at one time believed to be a diffusible stimulant, and it possibly may exert such an influence. In the acute nervous exhaustion of *typhoid pneumonia* we have once or twice seen it apparently act favorably in this way.

For reasons to be hereafter adduced (see page 438), it is certain that in poisonous doses phosphorus enters the blood in its elemental form. Wegner advances the following reasons for believing that therapeutic doses act as phosphorus upon the bony tissues. First, no similar action can be obtained from phosphoric acid unless from eight hundred to one thousand times the proportional dose be given. Second, the newly formed tissue is at first gelatinous. Third, there is no excess of phosphates in the bone. Fourth, when the food is deprived of lime the same new tissue arises, but remains in a soft, gelatinous state.

THERAPEUTICS.—The chief use of phosphorus in medicine is as a nutrient tonic to the nervous system. In all cases of chronic *nervous exhaustion*, whether involving the cerebral or the spinal centres, it is of great value ; even when the symptoms strongly suggest organic disease, as in threatening *cerebral softening* or *myelitic paraplegia* from excessive venery, it is often of service. It has been strongly extolled in *neuralgia* due to nervous exhaustion.

It is probable that it may be of value in some cases of impaired vitality, although the nervous system be not obviously implicated. H. Eames[3] states that he has obtained great benefit from its use in obstinate skin affections, such as *lupus*, *acne*, and *psoriasis*. S. R. Percy[4] has used it successfully for repeated *furuncular* eruptions. It has also been asserted to be useful in *cataract*.*

On account of its marked influence on the development of bone, Wegner suggested its use in *osteomalacia* and in *rickets*, and thereby started a large amount of clinical experimentation and a considerable clinical literature, in which there is some contradiction : the general result, however, has been to establish the value of the drug in rachitic cases, especially in those in which there is a tendency to *osteoporosis*. As large doses as can be borne without derangement of the digestion should be given.

TOXICOLOGY.—The ingestion of a fatal dose of phosphorus is not followed by any sensible effects for some time. After, however, from three to twelve hours a sense of weakness and of general wretchedness

* Tavignot (*Revue de Thérapeutique Médico-Chirurgicale*, August and September, 1871) and Gioppi (*Giornale d'Oftalmologia*, abstract in *N. Y. Medical Record*, 1872).

manifests itself, and in a large proportion of the cases (according to Lewin, eighty-eight per cent.) is accompanied, or soon followed, by vomiting. With the emesis there is nausea, and in most cases the patient soon complains of abdominal pain, the severity of which, however, never equals that of corrosive poisoning. The matters vomited consist of food, mucus, and bile. During the first eight or ten hours they often smell strongly of phosphorus, and are luminous in the dark. The vomiting may persist during the whole attack, but generally ceases on the second or third day, to reappear with the subsequent jaundice, when coffee-colored vomit from exuded blood is ejected. The pain, which in most cases abates with the vomiting, often spreads from the epigastrium over the whole abdomen, and in rare instances is paroxysmal. If it reappear in the latter stages, it is apt to affect especially the right hypochondrium, and is associated with decided tenderness in the region named and in the epigastrium.

In the very acute cases of phosphorus-poisoning a primary condition of pronounced cardiac weakness, passing into paralysis, may be present ;* in the subacute cases the heart-muscle undergoes so much degeneration that a slowly developed but progressive cardiac weakness is produced and may be the cause of death.

The tongue is whitish or abnormally red, sometimes furred. There are generally fever, loss of appetite, and thirst. Maukopff has noted a morning and evening temperature of from 37° C. to 39° C. and from 37.4° C. to 39.8° C. respectively. Later in the poisoning there is very often a remarkable fall in the temperature, which is generally, but not always, a precursor of death. The lowest point we have seen noted was 31.2° C. (88.2° F.) some hours before death.† In some cases fever is altogether absent, or comes on just before death.‡

The stools are at times normal in character and frequency, but there is general diarrhœa or constipation, with flatulence. Late in the attack the passages are in most cases very light clay-colored, or even whitish, and exceptionally they are bloody. In some cases they are phosphorescent.

Jaundice comes on in from thirty-six hours (cases reported by Maukopff[5] and by Tüngel[6]) to five days (Lebert and Wyss[7]) after the ingestion of the poison. In most cases it appears first in the conjunctiva, but sometimes the urine gives previous warning of its approach. In some cases there is with it a decided and palpable increase in the size of the liver, which may pass, if the patient live long enough, into an equally apparent lessening of the bulk of that viscus. The severe nervous symptoms are rarely, if ever, developed until after the jaundice, although early in the attack there are not infrequently anxiety, headache, giddiness, and dreamy unquiet sleep, or even sleeplessness. The more pronounced

* See especially J. Pal (*Jahrb. d. Wiener k. k. Krankenaushalten*, 1896, ix. 43).
† Battmann (*Archiv der Heilkunde*, 1871, 257).
‡ Concato (*Sydenham Soc. Year-Book*, 1869–70, 454).

nervous symptoms consist of delirium, which may be wild and is very frequently erotic, with somnolence ending in coma and death, occasionally preceded by convulsions. According to Taylor, the latter are a certain sign of approaching dissolution. Very generally, partial spasms and fibrillary contractions of the voluntary muscles occur, although there is always, in not too rapid cases, progressive paresis of the voluntary muscles. Death is usually put off beyond twenty-four hours, yet it has occurred in a child in four hours and in an adult in seven [8] hours ; also in nine [9] hours. The patient may suddenly succumb to collapse and cardiac paralysis, but more commonly dies comatose from a gradual failure of respiration and circulation.

If recovery occur, it is by a gradual amelioration of the symptoms, and the health of the patient is apt to be impaired for some time, the most marked disturbance usually being the digestive and nervous symptoms.* Apparently desperate cases will sometimes convalesce unexpectedly, and Tüngel states that a favorable issue may take place even after violent delirium.

The urine is almost always much affected by the poison. Very commonly it is scanty or albuminous, and sometimes it contains sugar. As was first pointed out by Munk and Leyden,[10] after jaundice has set in, bile-acids, as well as biliary coloring-matter, are always to be found in the urine. Not infrequently a cloudy sediment consisting in part of epithelial cells, often tinged with bile, is deposited. Oswald Kohts [11] and other observers have found leucine and tyrosine in the urine of dogs poisoned with phosphorus, and undoubtedly these substances are sometimes to be met with in the human excretion. The albuminuria generally follows, but may precede, the icterus. A very remarkable and apparently constant constituent of the urine is sarcolactic acid. Fat has been found in the urine inside of renal epithelial cells, and also as free globules (Schutz [12]).

Phosphorus induces in animals symptoms parallel with those commonly seen in man ; although Kohts states that he has seldom seen albuminuria in animals, even when the structure of the kidneys was profoundly altered. Orfila, Magendie, Munk, and Leyden found that the only effects following the injection of phosphuretted oil into the jugular vein of an animal were the exhalation of phosphoric acid and broncho-pulmonary inflammation : on examination (Munk and Leyden), oil, but no phosphorus, was found in the lungs. Ludimar Hermann and Alfred Brunner [13] have shown that in these experiments there was embolic arrest of the oil in the pulmonary capillaries, and consequent inflammation with subsequent oxidation of the phosphorus. When the phosphuretted oil is injected in the form of a fine emulsion, the characteristic symptoms and post-mortem appearances of phosphorus-poisoning result.

In some instances phosphorus-poisoning presents symptoms quite different from the typical array. Death may take place in a few hours,

* F. von Strausky has reported tetany as a sequela (see *Prag. Med. Wochenschr.*, xxii.).

and in such cases jaundice is not generally present.[14] Zeidler reports a death in forty-two hours, from suppression of urine, with collapse and erotic delirium. In a case of Bollinger's [15] the chief symptoms were vomiting, pain and tenderness over the abdomen, great weakness of pulse, gradually developed paralysis of the legs, and death, without jaundice, in four and a half days. The autopsy revealed hemorrhagic effusion between the membranes and the spinal cord, and also into the sheaths of the proximal portions of the spinal nerves.

In women, fatal doses of phosphorus very commonly produce a bloody pseudo-menstrual discharge, and when pregnancy exists almost invariably induce abortion or miscarriage. M. Miura[16] has found in the fœtus of poisoned rabbits structural changes similar to those of the mother.

The older toxicologists spoke of an erosive gastritis as a common result of phosphorus-poisoning, but it is now well established that such affection is very rarely induced by the drug.* As was first pointed out by Virchow,[17] there is universally a gastro-adenitis, which causes the gastric mucous membrane to become thickened, opaque, whitish, grayish, or yellowish white. Under the microscope the epithelial cells appear swollen and filled with granules and oil-globules, and in very advanced degeneration the cells completely break down. This gastro-adenitis is not due to a local action of the phosphorus, because it occurs when the poison is introduced through other channels than the mouth. The duodenum and intestines suffer similar changes. The liver is generally very much enlarged, friable, and light-colored ; sometimes it is mottled, and sometimes portions of it are deeply stained with bile.† The cells are gorged with fat-globules,‡ and in some cases there are small-celled interstitial thickenings due to hyperplasia of the trabecular tissue. The gall-bladder may be full or empty. In protracted cases the liver undergoes atrophy, with destruction of its secreting cells. According to the researches of Arthur Heffter,[18] the percentage of lecithin in the liver, which is fixed in

* It would appear probable that if it occurred at all it would be in rapidly fatal cases; yet Tüngel did not find it in a patient dead in nine hours of phosphorus-poisoning (*Virchow's Archiv*, 1864, xxx.).

† According to researches made by Emile Rousseau in the Pathological Laboratory of the University of Pennsylvania, the first anatomical changes in the liver occur in the centre of the lobules around the hepatic vein.

‡ A. Lebedeff (*Arch. f. Physiol.*, 1883, xxxi. 11) believes that the fat in the liver is not produced by degeneration of the hepatic tissue, but has simply been transported there from the subdermal regions. He bases this opinion upon his own observations,—first, that the phosphorus fat has the same chemical constitution as subdermal fat; second, in a dog which had been fed with linseed oil and then poisoned with phosphorus, the liver was loaded with linseed oil. This evidence is of very little value, because on the one hand the linseed oil probably accumulated in the dog's liver before the poisoning and simply remained over, and on the other hand there is no proof that fat produced by degenerative changes necessarily differs in composition from other fat. The fact that the liver and other organs are destroyed in phosphorus-poisoning may be considered proof that the fat is formed out of the affected tissue ; although this seems contrary to the allegation of Bergeat (*Gesellsch. f. Morph. u. Physiol. München.*, 1888), that in very emaciated animals the phosphorus-poisoning may run its course without the formation of fat.

health, is greatly lessened in phosphorus-poisoning. The kidneys, especially in their cortical portion, suffer a degeneration similar to that of the liver, the epithelium becoming enlarged, granular, fatty, and finally undergoing destruction. In some cases, even with the naked eye, yellowish streaks can be seen following the course of the urinary canals, from the papilla into the cortex. These are due to epithelial fatty degeneration, and have been thought to be pathognomonic of phosphorus-poisoning; but Paltauf has shown that they may be at least simulated in other conditions. The voluntary and cardiac muscles, the spleen, the lungs, and probably all the tissues partake of the universal fatty degeneration* which Wegner has shown to involve even the minute arterioles.

The nervous system does not escape. As long ago as 1880 Danillo declared that he had found a myelitis in phosphorus-poisoning, and Gurrieri[19] has discovered in the poisoned dog degenerations of various portions of the spinal cord; whilst it has been shown by Uziemblo† that profound alterations take place in the retina, which becomes œdematous, with marked alterations in the vessels, hemorrhagic extravasations, and necrotic degeneration of the nervous cells.

The blood is often profoundly affected,‡ becoming very dark, losing its power of coagulation, and apparently suffering also in its corpuscular elements; for ecchymoses are almost universal, and hæmatin crystals are occasionally found in the viscera. The loss of coagulability is not always complete, and is usually most pronounced in the subacute cases.§ In the case of Concato the white corpuscles were observed during life to be increased in number, and the red to be diminished in size and altered in form. The ecchymoses occur in all parts of the body, but are apt to be especially pronounced in the mediastinum and the serous membrane. Schiff[20] has found that in dogs, after death from phosphorus, the blood does not pass into the veins, but remains in the arteries. O. Silber-

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* For a full discussion of the pathology of phosphorus-poisoning, see H. Lebert and O. Wyss (*Archives Gén.*, September, 1868), Otto Bollinger, also O. Kohts (*Deutsches Archiv f. Klin. Med.*, 1869, v.), Ziegler (*Beiträge Path. Anat.*, ii.), G. Kronig (*Virchow's Archiv*, 1887, cx.), Aufrecht (*Deutsch. Arch. Klin. Med.*, 1897, lviii.), Hans Schmaus (*Münchener Med. Wochensch.*, 1897, xliv., also 1898, xlv.), Hans Schmaus and Arthur Boehm (*Arch. f. Path. Anat.*, 1898, clii.). For an important collection of recent papers, see *Schmidt's Jahrbücher*, cclvii., 94.

† See Uziemblo (*Die Pathologischen Alterationen der Retina bei Phosphovergiftung*, Monographie, St. Petersburg, 1892, russisch), also Julius Steinhaus (*Beiträge zur Pathologischen Anatomie und zur Allgemeinen Pathologie*, xxii.).

‡ Mayer states that when very large doses of the poison have been taken the blood and even the urine (?) may be phosphorescent (*Canstatt's Jahresbericht*, 1862, v. 123). Otto Taussig, as the result of a series of blood studies in phosphorus-poisoning, reaches the somewhat remarkable conclusion that in man, usually at about the acme of the symptoms, there is either a suddenly developed or a slowly produced increase of the red blood-corpuscles, without an increase of the hæmoglobin of the blood and with a distinct lessening of the leucocytes, whereas in the rabbit there is no alteration in the amount of hæmoglobin or number of red disks, but a plain increase of the white corpuscles; and in chickens there occurs an enormous destruction of the red disks, with a marked leucocytosis (*Archiv f. Exper. Path. u. Pharm.*, 1892, 30).

§ See Corin and Ansiaux (*Viertelj. f. gerichtl. Med.*, 1894, vii.).

mann [21] states that thrombi are formed in the blood-vessels; and it has been shown by G. Puppe that these are very common in slow cases of the poisoning, and are of fatty nature.

It should be remembered that although some or all of the lesions which have just been described are usually found in the bodies of persons dead of phosphorus-poisoning, it is possible for the poison to take life very rapidly and leave no trace of its influence, there being not even sarcolactic acid in the urine (see case reported by Paltauf [22]). According to the researches of W. W. Podwyssotsky,[23] in rapid cases the first change in the body consists in the formation of little whitish-yellow necrotic foci in the liver. The anatomical changes in the liver in phosphorus-poisoning are sufficient to confirm the statements of Schultzen and Riess, that in the poisoning there is arrest of glycogen and sugar formation.

The elimination of bile acids in the urine shows that the jaundice of phosphorus is caused not by an arrest of secretion, but by an occlusion of the biliary passages and consequent resorption of the bile.* O. Kohts has apparently demonstrated that the occlusion is most frequently due to the duodenitis involving the common duct, so as to obliterate its lumen by the swelling of the mucous membrane. In some cases, however, it is probable, as believed by Wyss, Alter, and Ebstein, that a catarrhal inflammation of the minute gall-ducts is the cause of the jaundice, and also that the result is in part effected through pressure upon those ducts by the swelling of the glandular and trabecular tissue.† It is proper to state that Demarbaix [24] and Willmart [25] insist that the icterus is not really hepatogenous, but hæmic in origin, chiefly because they have found hæmatoidin in the urine. This fact, however, proves only that the blood is altered by the poison: it does not disprove the liver origin of the jaundice.

Acute phosphorus-poisoning so closely resembles yellow atrophy of the liver that their clinical distinction is sometimes difficult, nay, impossible. Distinct phosphorescence in the breath, vomit, or stools would, of course, be direct evidence of poisoning. This phosphorescence, however, very often cannot be detected: according to Vetter,[26] it can be rendered more evident in the vomit, stools, etc., by acidifying with sulphuric acid and warming in a shallow dish. When death ensues during the first week of phosphorus-poisoning, the enlarged liver affords a distinctive proof of poisoning; but when the case is more protracted, the atrophied liver of phosphorus cannot be distinguished from that of the natural dis-

* E. Stadelmann (*Archiv f. Exper. Path. u. Pharm.*, 1888, xxiv.) states, as the result of his experiments made upon dogs, that so far as the secretion of bile is concerned three stages can be made out. In the first stage there are irritation of the liver and increase of the formation and excretion of biliary coloring-matter; in the second stage the gall becomes mucous and cloudy, and the production and separation of biliary coloring-matter are lessened (it is in this stage that the icterus begins); in the third stage the gall becomes again clear, dark, and more rich in biliary coloring-matter, so that the normal excretion of biliary coloring-matter is notably surpassed.

† For an elaborate discussion of the cause of jaundice, see Kohts's paper (*Deutsches Archiv f. Klin. Med.*, v. 168); also that of Bollinger (*Centralbl. f. die Med. Wiss.*, 1869, and *Deutsches Archiv f. Klin. Med.*, 1869. v.).

ease. Phosphorus-poisoning usually develops more abruptly than does acute yellow atrophy, and the primary disturbance of the stomach is more severe, whilst the lull of the symptoms is more complete. The clinical differences, however, between various cases of either affection are greater than those which have been relied upon as separating the two affections. Köhler has asserted that oxymandelic acid in atrophy of the liver replaces the sarcolactic acid of phosphorus-poisoning, and stress has been laid upon the asserted facts that in the natural disease leucine and tyrosine are present in abundance in the urine, while in the poisoning they are absent. In yellow atrophy, however, tyrosine is not infrequently absent from the urine and leucine present in very small amount, while both principles may be present in phosphorus-poisoning.* In regard to the acids in the urine, very careful chemical analysis would in any case be necessary to determine their presence, and sufficient evidence is certainly not yet forthcoming to show that either of them is really characteristic. Chemical examination is therefore absolutely necessary in all medico-legal cases.† According to M. Poulet,[27] phosphorus is eliminated as hypophosphoric acid, and the poisoning can be recognized by heating the urine with nitric acid to calcination. If hypophosphoric acid be present, as dryness is reached the mixture suddenly bursts into a flame like a packet of matches.

It has of late years been demonstrated that phosphorus passes into the blood as phosphorus, and not in the form of phosphoric acid or other compound.

In poisoning cases in men the breath is said sometimes to be distinctly phosphorescent, and in animals Bamberger has found phosphorus in the blood and Husemann and Marme in the liver two or three hours after its ingestion. W. Dybkowsky[28] has detected it in the blood and liver ten hours after its ingestion, and other observers have demonstrated its presence in almost all of the tissues. It seems probable that to some extent it finds entrance into the circulation by being dissolved in the various fatty matters contained in the alimentary canal. At the temperature of the body, however, it yields abundant vapors, and Bamberger has demonstrated that these readily and rapidly pass through animal membranes. He has found that defibrinated blood, when separated from the fumes of phosphorus only by an animal membrane, rapidly becomes saturated with the poison. Dybkowsky has confirmed this, and it cannot be doubted that in a similar manner living blood absorbs the poison from the alimentary canal. W. Dybkowsky's research renders probable the theory of Schuchardt[29] that the phosphorus to some extent in the alimentary canal, but much more largely in the veins, is converted into phosphuretted hydrogen, and that some of this compound and some of the phosphorus

* Cases (*Wiener Med. Presse*, 1872; *Schmidt's Jahrb.*, clxix. 127, cxcv. 123). Ossikovsky believes that the principles appear habitually about the sixth day of the poisoning, when the liver is still enlarged.

† For discussions of the diagnosis between yellow atrophy and phosphorus-poisoning, see Köhler (*Syd. Soc. Year-Book*, 1870, 455), Schultzen and Ries (*Annalen des Berlin. Krankenhauses*, 1869, xv.), and especially I. Ossikovsky (*Wien. Medizin. Presse*, 1872, xiii., abstracted in *Schmidt's Jahrb.*, cliv. 15). For cases in which the question was legally raised, investigated, and discussed, see *Schmidt's Jahrb.*, cxli. 167; *Syd. Soc. Year-Book*, 1832, 430; *Annales d'Hygiène*, Jan. 1869.

itself is oxidized in the venous blood, so that phosphoric acid, besides phosphorus and phosphuretted hydrogen, is emptied into the arterial blood; further, that the last two compounds are oxidized at the expense of the arterial blood and the tissues it feeds, and that the poisoning is due to this deprivation of oxygen. For the details of the experiments upon which these conclusions rest we must refer the reader to the original memoir.*

The cause of death in phosphorus-poisoning is probably the widespread structural alterations, as the experiments of A. Hauser[30] indicate that the poison does not act by inhibiting life processes.

The indications for treatment in phosphorus-poisoning are very evident. It is plain that no medication can influence the terrible organic lesions induced, and that the primary object must be to prevent the absorption of the poison. Emetics and purgatives are, therefore, of prime importance. The necessity of the persistent use of evacuants is shown by the finding of phosphorus by Starck[31] in the stools three and a half days, and in the vomit two days, after the ingestion of the fatal dose. As phosphorus is soluble in oils, *no fatty matters* should be allowed either in the food or in the medicines. As an emetic, *copper sulphate should always be chosen.*

The minute particles of phosphorus adhere so closely to the alimentary canal that they cannot be dislodged by mechanical means, and an antidote is urgently demanded. For the purpose of oxidizing the poison, Duflos suggested calcined magnesia and chlorine-water, and Scherer the chlorinated lime; but in practice these substances have been found of no value, on account of the slowness of their action.

The oil of turpentine, originally proposed by Andant[32] as an antidote to phosphorus,† has been largely used by experimenters, with apparently contradictory results, which, as is now known, were due to the employment of different varieties of the oil.

There are in European commerce three varieties of turpentine,—the rectified, the German, and the French. Jonas[33] found that while the pure oil has no effect upon phosphorus, the acid French oil forms with it a crystalline, spermaceti-like mass. This is soluble in ether, alcohol, and alkaline solutions, and has received the name of *turpentine-phosphoric acid.* It is said to be eliminated by the kidneys unchanged, and to exert no deleterious influence. The elaborate experiments of Vetter on dogs and rabbits gave results in accord with these facts, for he found the rectified and German oils to be of no value in phosphorus-poisoning, while the crude acid French oil was distinctly antidotal. Kochler, however, asserts that when the German oil has not been rectified for some time, it acts upon phosphorus. He believes that the oil acts partly by oxidizing the poison and partly by converting it into the harmless turpentine-phosphoric acid. One part of the oil must be given for 0.01 part of the phosphorus.[34] Case of recovery.[35] See also Bène.[36]

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* M. Lecorché (*Archives de Physiologie Normale et Pathologique*, 1868, i., 1869, ii.) believes that phosphorus acts in the blood as phosphoric acid, but does not establish his opinion. For a discussion of this, see Dybkowsky's paper.

† For cases, see *Gazette Hebdomadaire*, 1874; *Schmidt's Jahrbücher*, clxix. 126; *Med. Times and Gaz.*, 1876, ii. 461.

Ordinary American oil of turpentine and Canada balsam are of *no value* in phosphorus-poisoning.

As was pointed out by Eulenburg and Guttmann,[37] and subsequently by Bamberger,[38] phosphorus in a solution of a soluble salt of copper becomes immediately black, owing to the formation of a phosphide of the metal. Bamberger also asserts that, while this change is very rapid, that induced by turpentine is a slow one, and, from an elaborate series of experiments upon animals, concludes that copper is much the more valuable and certain antidote. Antal appears to have been the first to use potassium permanganate as an antidote to phosphorus, and in a series of experiments upon dogs E. Q. Thornton[39] found it much superior to cupric sulphate. Hydrogen dioxide appeared in Thornton's experiments to be valueless. In human poisoning cupric sulphate should be given in dilute solution, three grains every five minutes until vomiting is induced. After this the potassium permanganate should be freely administered, or, as was successfully done by Hajinos, the stomach may be washed out with its solution; later, the magnesium sulphate or citrate may be given as a quickly acting purge, and symptoms met as they arise.*

Chronic Poisoning.—Match-makers and other artisans who are exposed by their occupations to the fumes of phosphorus suffer from chronic poisoning, which is especially distinguished by the occurrence of necrosis of the upper or lower jaw. It occurs chiefly in those artisans who have bad teeth, and the experiments of Wegner have demonstrated that the necrosis of the jaw is due to the local action of the vapor of phosphorus.

Wegner found that when rabbits were kept in an atmosphere full of the fumes of the poison no necrosis ever occurred, unless, by means of an unsound tooth or an artificial wound, the atmosphere had access to the bone. If such access were, on the other hand, allowed to any bone of the body, periostitis and subsequent

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* We have allowed the text to stand as in the old edition because of the present uncertainty as to the comparative values of the use of copper sulphate and potassium permanganate. In the United States phosphorus-poisoning is very rare, we never having met with a report of more than one or two cases. In Continental Europe, however, probably on account of the difficulty of obtaining poisons through the restrictions of the law, phosphorus is perhaps the most used of any poison for the purpose of suicide. Thus, out of forty cases of attempted self-murder, brought to the Prager clinic between 1889 and 1895, in thirty-nine the phosphorus contained in the heads of matches had been employed (Fr. Lanz, *Berl. Klin. Wochenschr.*, 1895, xxxiii.). Formerly the treatment at the clinic consisted in washing out the stomach with warm water until the smell of phosphorus disappeared; then continuing the washing with water containing copper sulphate and calcined magnesia, and following up by giving internally copper sulphate and old oil of turpentine; also large doses of sodium bicarbonate. Since 1893, when the Antal method was introduced, the plan has been to wash out the stomach with large quantities of one-eighth per cent. of the permanganate; then administer one litre of the one-half per cent., at the same time giving a purgative; on the following day giving large doses of sodium bicarbonate with the oil of turpentine. The mortality per cent. of the cases before the change of treatment was 36.6, since the change of treatment 41.6,—a result which is not favorable to the newer method.

necrosis resulted. Further, when rabbits received continuously small doses of the phosphorus by the mouth, no necrosis occurred even after wounds which laid bare the bones.

ADMINISTRATION.—The best preparation of phosphorus is the elixir (ELIXIR PHOSPHORI, U. S.), one drachm of which contains about one-sixty-fifth of a grain (0.001 Gm.) of phosphorus. Dose, twenty to forty minims (1.2–2.5 C.c.). Phosphorated oil (OLEUM PHOSPHORATUM, U. S.) contains one-hundred-and-fifteenth of a grain of phosphorus to the minim. Dose, one to three minims (0.003–0.18 C.c.). Each pill of phosphorus (PILULÆ PHOSPHORI, U. S.) contains about one-hundredth of a grain (0.0006 Gm.).

The dose of phosphorus may be set down as from the one-hundredth to the one-fiftieth of a grain, increased unless gastric disturbance is produced. J. A. Thompson affirms that he has given one-fourth of a grain every four hours without injury. Anstie says that he has seen slight poisoning produced by three-fourths of a grain taken in seven days in divided doses. It is always wiser to have a freshly made preparation, as phosphorus in solution or in pill is very prone to undergo oxidation.

ZINCI PHOSPHIDUM. U. S.—*Zinc Phosphide* has been largely used, with asserted good results, as a substitute for phosphorus. According to the researches of Vigier,[40] it would seem that the phosphide yields its phosphorus within the economy, probably to form a phosphuretted hydrogen. He found that it killed rabbits more quickly than did a corresponding dose of phosphorus, and that both symptoms and lesions were identical in the two cases. The phosphide should be given in pill or granule. Dose, one-twentieth to one-twelfth of a grain (0.003–0.005 Gm.). Seguin recommended doses of one-sixth to one-fourth of a grain (0.016–0.01 Gm.).

ACIDUM ARSENOSUM—ARSENOUS ACID. U. S.

White Arsenic, *Arsenic*, or *Arsenic Trioxide*, as first prepared by sublimation from the ores, is in transparent masses, but on keeping becomes milk white externally. It is soluble in water, has a vitreous fracture, is odorless, of a faint sweetish taste, and volatilizes without fusion "at a temperature of 424.4° F." When it is put upon red-hot iron it emits a garlicky odor, owing to its being first reduced to a metallic state and then volatilized.

PHYSIOLOGICAL ACTION.—*Local Action.*—When in concentrated form arsenic is a powerful though slowly acting escharotic, and even when well diluted is a violent irritant. Although it has the property of preserving animal tissues almost indefinitely, and is a violent poison to all forms of life, it acts proportionately much more powerfully upon the higher than upon the lower organisms. The solution of one part in thirty thousand, it is said, will kill seeds, whereas fungi will grow in organic solutions containing as much as one per cent. of potassium arse-

nite. According to Johannsohn,[1] it is capable of causing a peculiar degeneration of the yeast-plant, although it actively increases the production of bacteria in yeast; and in lactic fermentation the growth of the fungus is checked by it, whilst that of the ordinary mould is favored.* Its action is so much greater upon the tissues of higher animals than upon the lower organisms that it cannot be classed among the practical germicides. Johannsohn and Schaefer and also Boehm[2] state that it exerts no influence upon non-organized ferments, either vegetable or animal, such as amygdalin, pepsin, and pancreatin.

Absorption and Elimination.—Although when arsenic is taken into the stomach in lumps it may be absorbed so slowly as to escape in part through the alimentary canal, when it is taken in powder, and especially when it is in the form of the soluble salt, it is absorbed with rapidity.

It is so readily taken up that its free external use and its employment as an escharotic are accompanied by distinct danger. Six cases are on record in which severe or fatal poisoning has been produced by the introduction of it into the vagina.†

It is eliminated chiefly by the kidneys, although it is thrown off freely when in toxic amount by all the excretory glands and mucous membranes but especially by those of the gastro-intestinal tract.

M. G. Bouchet and Lewald in independent researches found arsenic in notable quantities in the milk of nursing women.‡ Unterberger has detected it in the alimentary canal of animals poisoned by injection into the vein. M. Chatin has found it in the serosity of a blister, Bergeron and Lemaître[3] in the sweat, and Taylor[4] in the contents of the stomach of a child poisoned by its application to the scalp.

The single dose escapes rapidly from the body, elimination being usually complete in from a few hours to three or four days. When in large amount it may remain long in the body.

Flandin and Danger[5] failed, three days after the last dose, to detect arsenic in the bodies of animals to which fifteen grains had been given daily; and in a child killed in two days by an arsenical pigment, none of the metal could be found in the body.[6] In the great majority of instances, however, there is no trouble in finding arsenic in the bodies of those poisoned by it, and Steinhäuser[7] reports a case in which it was detected in the remnants of a corpse that had been buried for twenty-two years. Further, it would appear that the failure to find arsenic has often depended upon the lack of delicacy in the chemical operations. Using the chemical method devised by Charles R. Sanger, E. S. Wood[8] has been able to detect arsenic in the urine ninety-three days after the taking of a single toxic dose, and from six to eighty days after mild courses of Fowler's solution.

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* Various observers have endeavored to determine which tissues contain most arsenic after death from the poison, with such varying results as practically to demonstrate that there is no uniformity of deposition in the various cases. Consult *Arch. de Physiol. Norm. et Path.*, 1875, ii. 653; *Chem. Centralblatt*, 1879, 602; *Arch. f. Exper. Path. u. Pharm.*, xiii. 257; *The Chemist and Druggist*, 1879, xxi. 381; *Comptes-Rendus*, lxxxviii. 1212.

† See A. Haberda (*Wien. Klin. Wochenschr.*, 1897, x. 9, 201).

‡ See *American Practitioner*, 1887.

General Action.—When a single dose of arsenic of just sufficient size to be felt is ingested, colicky pains, diarrhœa, and perhaps nausea result. After a very large toxic dose, in from one-quarter to three-quarters of an hour an intense burning pain is felt in the œsophagus and stomach, soon spreading to the whole belly, and often accompanied by a sense of constriction at the throat and an acrid, metallic taste. In a very short time violent vomiting and purging come on. The matters rejected are at first mucous, and variously colored by the contents of the primæ viæ; but they soon become bilious, often yellowish or greenish, and finally serous, with mucoid flakes and a greater or less amount of blood. As the case progresses, the symptoms mentioned increase in intensity, and to them are soon added others of different nature. The thirst is excessive; the urine is suppressed; the extremities are icy cold; the pulse is small, feeble, and frequent; the rapid and labored respiration is very much embarrassed and painful from the abdominal tenderness; the surface is dark and cyanosed; violent cramps add their torture; exhaustion deepens into collapse; convulsions or coma ensue, and death occurs in from five to twenty hours.

In another set of cases, when the dose has been smaller or the subject less susceptible, the termination is not reached so soon. After symptoms similar to but less violent than those just described have lasted from a few hours to one or two days, a remission occurs; the purging and vomiting grow less frequent, or perhaps intermit; even the abdominal tenderness may in great measure disappear; but the persistent thirst, cold extremities, and albuminous urine show that the danger is not past, and after a time the case puts on a more alarming aspect. Fever develops, the tongue becomes dry and red, the belly very tumid, the abdominal pain more severe, dyspnœa and cyanosis come on, the face is swollen, nervous symptoms, tremblings, cramps, and convulsions appear, and finally an icy coldness pervades the frame, and death occurs in from two to six days. The mind is generally clear to the last. An eruption very frequently appears, sometimes as early as the second day, sometimes not until the fifth. Its character is various: thus, it may be petechial, urticaria-like, papular, vesicular, or pustular.*

Such are the ordinary phenomena of acute arsenical poisoning; but anomalous cases are not very rare. Immediate profound collapse, without abdominal pain, is said to have been the chief manifestation in some cases. We have seen heavy sleep as the most marked symptom, the sleep, however, being interrupted at intervals by wild outcries and writhings, evidently the outcome of abdominal pain, although no statement could be obtained from the patient. Again, serous purging may be the chief symptom, and arsenical poisoning has been mistaken for cholera, not only during life, but also on the post-mortem table.†

* See Imbert-Gourbeyre (*Moniteur des Hôpit.*, 1857), also A. Huber (*Zeitschr. Klin. Med.*, 1888).

† See *Virchow's Archiv*, 1870, l.

When arsenical poisoning is not fatal, the convalescence is apt to be slow and interrupted by various disorders. Prominent among these are affections of the alimentary canal, due to the structural changes produced by the poison. Nervous symptoms are common, and may affect the motor or sensory sphere separately or combined. In some cases they have developed very suddenly.[9] We have seen anæsthesia of the feet as the only symptom ; motor paralysis may exist alone, but it is usually accompanied by anæsthesia, hyperæsthesia, loss of temperature-sense, great feeling of coldness, or other disorder of sensation, and not rarely excessive pain, which may be aching or lancinating. Occasionally there are severe cramps. Normal sensibility is usually regained before normal motility. Of one hundred cases of arsenical paralysis collected by Imbert-Gourbeyre,[10] in more than half all the extremities were affected ; about one-fourth were paraplegic ; in the remainder there was hemiplegia or local palsy. Most frequently the paralysis was not pronounced above the elbow or knee. The lamed muscles are usually sensitive to pressure* and undergo rapid atrophy, losing very early their electro-muscular contractility, or presenting the "reactions of degeneration." The tendency towards more or less complete recovery is remarkable. We have seen recovery when the muscular remnants on the wasted limbs had for many months been unable to respond to any form of galvanic current ; and out of Imbert-Gourbeyre's one hundred cases all got well except three.

N. Popoff[11] found, in dogs killed in a few hours by a dose of arsenic, the spinal cord inflamed ; after slower poisoning there were masses of "exudate" in the neighborhood of the blood-vessels, and in very protracted cases the walls of the spinal arterioles were found to be thickened and the large cells of the gray matter profoundly altered. The protoplasm first became opaque and granular ; the nuclei grew fainter and fainter, and disappeared ; vacuoles appeared, and encroached more and more on the shrunken body of the cell, which finally melted down. In the elaborate experiments, however, of C. Alexander[12] upon rabbits, the spinal cord was found to be healthy, but the nerve-trunks were in a condition of degenerative atrophy, and the muscles themselves had undergone changes which were believed to be the result of coagulation-necrosis.

That arsenic is capable, in man, of producing a myelitis especially affecting the multipolar cells of the cord is shown by the autopsy reported by Erlicki and Rybalkin.[13] In this case there was no tenderness of the nerve-trunks, so that there appear to be two forms of arsenical paralysis, —one due to myelitic change, the other to a wide-spread multiple neuritis, —the diagnosis between the two being made by the presence or absence of nerve-tenderness. It is very probable that in some cases both lesions are present.† In some of these cases trophic changes are pronounced :

* Consult C. Gerhard (*Sitzungsb. Physik. Med. Gesellsch. Würzburg*, April, 1882), Renner (*Ueber ein Fall von chron. Arsenvergift.*, Würzburg, 1876), W. P. McIntosh (*N. Y. Med. Record*, Feb. 1885, 145), Seguin (*Journ. Nerv. and Ment. Diseases*, Oct. 1882, vii. 665), and C. K. Mills (*Trans. College of Physicians of Philadelphia*, 3d series, vi. ; *Archives de Physiol. Norm. et Path.*, 1884, iv.).

† See also *Wiener Klin. Wochensch.*, 1891, iv.

thus, we have seen a growth of hair several inches long cover the wasted limbs. If in any case of arsenical paralysis there were no sensory disturbance, the probabilities would be very strong that the lesion was a toxic poliomyelitis.

We know of no general studies upon the blood of human beings poisoned with arsenic.*

S. Bettmann[14] has shown that in the rabbit in subacute arsenical poisoning there is a marked lessening in the number of the red blood-corpuscles and in the percentage of hæmoglobin, without any distinct change in the general percentage of leucocytes, although the lymphocytes increase and the eosinophilen cells decrease. Late in the poisoning nucleated red blood-corpuscles may be found in the circulating blood.

The most obvious lesions found after death from acute arsenical poisoning are those of severe gastro-enteritis, but often there is also a widespread granular or fatty degeneration of the tissues.

The gastric mucous membrane is usually swollen, maculated with patches of a deep crimson or more commonly brownish-red color, and is often softened and covered with a diphtheritic exudation, but is rarely ulcerated. Perforation is exceedingly uncommon. The mucous membrane of the upper part of the small intestine, and sometimes of the whole of it, is in a condition similar to that of the stomach. In some cases the lesions very closely resemble those of cholera, as was first pointed out by Virchow.[15] In the microscopic examination of a cadaver whose bowels were filled with a "rice-water" fluid, that observer found in the intestinal contents epithelial flakes and the fungus described by Klebs as peculiar to, and, indeed, the cause of, cholera. The epithelial cells of the mucous membrane were choked with granules, many of them in an advanced stage of fatty degeneration; the interstitial tissue was full of large round granulated cells; the solitary glands and Peyer's patches were very much swollen. These facts have been confirmed by Hoffmann.[16] The gastro-intestinal lesions produced by arsenic are not due solely or largely to its immediate local effect, since they occur equally when the animal is killed by injection of the poison into a vein. The local influence of the drug is, however, probably not altogether lost, since Unterberger found that a larger dose was required to kill an animal by venous injection than by exhibition by the mouth. Curious and at present unexplainable anomalies occur in the distribution of the gastro-intestinal inflammation, and autopsies have been reported in which the stomach has altogether escaped.

M. Karajau[17] reports a case which had been mistaken during life for acute atrophy of the liver; Fr. Grohl and Fr. Mosler[18] one in which they found fatty or granular metamorphosis of the glands and epithelium of the stomach and intestines, of the cardiac muscle, of the diaphragm, of the cortical portions of the kidney, and, to a slight extent, of some of the voluntary muscles; I. I. Pinkham[19] one in which the liver, kidneys, and epithelial lining of the peptic glands were almost destroyed; similar lesions have also been reported by M. V. Cornil[20] and by Féréol.[21]

As was first pointed out by Salkowsky,[22] when the animals are poisoned by a small dose of arsenic, so as to live from three to six days, the liver† becomes much

* For a spectroscopic study of the effect of arsenic upon the coloring-matter of the blood, see *Centralblatt*, 1868, 609. It is interesting here to note that arsenic, antimony, phosphorus, and ammonia act very similarly, if not identically, upon the blood.

† Salkowsky also noted that early in both arsenical and antimonial poisoning the glycogenic function of the liver is abolished. Podwyssotsky finds that the first change

enlarged and very fatty.* On microscopical examination, the cells on the exterior of each acinus are natural ; those in the centre in the most advanced stages of degeneration. The kidneys are similarly affected,—their tubes choked up with fat-globules, their epithelium almost completely destroyed. The muscles of the heart and diaphragm are also compromised.

In frogs poisoned with arsenic the epidermis peels off from the derm, as was first noted by Ringer and Murrell, and Emily A. Nunn[23] has found that the influence of the poison is first manifested in the under portion of the epidermis, the degeneration progressing from the derm outward.

In some cases of arsenical poisoning yellow patches, believed to be due to the formation of arsenical sulphides, have been noted on the mucous membrane of the stomach and intestines. Similar yellow deposits were found by Chunilal Bose[24] on the endocardium. It is probable that in these cases the sulphide is formed after death by the aid of putrefactive gases.

As arsenic is never used in medicine for an acute effect, the chief interest to the therapeutist centres around its physiological action when given in small doses ; yet it seems necessary here to take cognizance of the physiological action of large amounts of the poison.†

Nervous and Muscular Systems.—The symptoms of arsenical poisoning in man show that the drug has a marked influence upon the nervous system.

In the frog arsenic acts as a paralyzant of the nerve-centres. W. Sklarck,[25] of Berlin, states that the small dose causes in the frog cessation of voluntary movement, with complete loss of sensibility to chemical and mechanical irritants at a time when the animal will struggle actively to recover its position if laid upon its back. Tying of the iliac artery had no effect in preserving motion or sensibility in the protected leg. It would appear, therefore, that the cessation of voluntary motion was due to a complete paralysis of the centres of common sensation, probably up to the perceptive centre in the brain ; the frog, placed upon his back, being induced to struggle into the normal position by sensations received either through the special senses or possibly through the muscular sense. The researches of Ringer and Murrell[26] upon frogs have given very different results from those just described, they finding that the symptoms of poisoning came only after the lapse of some hours, and that paralysis of voluntary motion preceded that of sensation and reflex action.

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produced by overwhelming doses of arsenic consists of the formation of necrotic foci in the liver (*St. Petersburg Med. Wochensch.*, 1888). O. Silbermann believes that during life thrombi form in various portions of the body (*Archiv Path. Anat.*, cxvii.). For further discussion, see Ziegler (*Beiträge Path. Anat.*, ii.), also M. Wolkow (*Archiv f. Path. Anat. u. Phys.*, 1892, cxxvii.).

* According to T. Araki (*Zeitschrift f. Physiol. Chemie*, 1892, xvii.), arsenical poisoning is related to phosphorus-poisoning, not only in the occurrence of fatty degeneration of the liver, but also in the appearance of lactic acid in the urine.

† The theory of Binz and Schulz, that arsenous acid acts by taking from protoplasm oxygen, so as to be converted into arsenic acid, and afterwards yields this oxygen to oxidize the protoplasm, and then repeats the process, seems to be so illy supported that in regard to it the reader is simply referred to *Arch. f. Exper. Path. u. Pharm.*, xi., xiv., xxxvi., xli. ; also *Brit. Med. Journ.*, 1882, ii. 1135. Dogiel's theory, that arsenic unites chemically with the albuminous principle, is more probable. (See *Trans. International Congress*, 1884, i. 134.)

Ringer and Murrell suggest that these differences of result depend upon the time of year at which the frog was experimented on.

There is accord between the experimenters in regard to the cause of the final arsenical paralysis, all finding that it is produced by a direct action of the poison upon the nerve-centres. Ringer and Murrell have, however, further shown that the nerves and muscles do not entirely escape the poison, which is toxic to all highly organized tissues.

Circulation.—The toxic dose of arsenic greatly lessens the rate and force of the pulse-beat and markedly lowers the blood-pressure. Sklarck found that in the isolated frog's heart arsenic produces slowness and feebleness of pulsation, ending in a diastolic arrest, after which immediate galvanic or mechanical irritation caused imperfect systolic movements. It would appear, therefore, that the toxic dose of arsenic is a direct cardiac depressant; but as both Cunza and Unterberger[27] have found that in arsenical poisoning the heart persists in its movements after the cessation of respiration, it is evident that arsenic is more powerful as a respiratory than as a circulatory poison. Further, as demonstrated by Unterberger, the lowering of the arterial pressure in arsenical poisoning is very largely due to a vaso-motor paralysis.

Thus, Unterberger found that in an animal under the influence of the poison neither galvanization of a sensory nerve nor of the vaso-motor centre in the upper cord had any influence upon the force of the blood-current. Galvanization of the splanchnics had no effect upon the arterial pressure,—apparently showing that the vaso-motor palsy was peripheral; but Unterberger found, to his astonishment, that stimulation of the cervical sympathetics had the usual effect upon the vessels of the rabbit's ear. Supposing these observations to be correct, there are only two seemingly possible methods of reconciling them: either the drug acts upon the peripheral vaso-motor nerves in the abdomen and not upon the same nerves in the neck, or else there is during arsenical poisoning such depression of the power of the cardiac muscle that narrowing of the blood-path does not have the usual effect. Unterberger found that compression of the abdominal aorta was followed by a great rise of pressure, and therefore he believes that the heart in arsenical poisoning has not lost its power. Some complicated transfusion experiments which he made indicated differently; so that while his proposition that arsenic paralyzes the peripheral vaso-motor nerves of the abdomen and not those of the head may be considered probable, it certainly is not proved. It would be a very easy matter to decide the question by dividing the splanchnic nerves in a poisoned animal: if the reduction of the arterial pressure be really due to an abdominal vaso-motor paresis, section of the splanchnic should have no effect on it.

Tissue-Change.—Schmidt and Stürzwage believe that arsenic markedly influences tissue-change, because they found in rabbits a decided diminution in the excretion of carbonic acid and of urea during the use of minute doses of the poison. Fokker,[28] however, was unable to perceive in three experiments that daily doses of from .15 to .075 grain of arsenic to a dog had any effect upon the elimination of urea, and Kossell and Gaethgens,[29] in two experiments, have noted a very decided increase of the elimination of urea produced by toxic doses of arsenic in

the dog. The recent experiments of Chittenden and Cummins[30] are in accord with the early results of Stürzwage, as they found that in the case of rabbits arsenous acid has a tendency to diminish the elimination of carbonic acid. The evidence which we have at present is not sufficient to warrant a positive opinion, but it indicates that *small doses of arsenic check tissue-change and decrease nitrogenous elimination, while large toxic doses have the opposite effect.*

Action of Small Doses.—Minute quantities of arsenic may be given for a long time without perceptible effect. When the dose is increased, active manifestations of gastro-intestinal irritation may appear, such as loss of appetite, nausea, abdominal pain or uneasiness, diarrhœa, and perhaps sympathetic headache. By the use of frequent small doses these symptoms may generally be avoided, and what may be termed the constitutional action of arsenic be obtained. The first sign of this is generally a puffiness about the eyes, at first visible only in the early morning, but soon increasing into decided œdema, which after a time may lose its local character and the patient be involved in general anasarca. This anasarca, as was, we believe, first pointed out by S. Weir Mitchell,[31] may or may not be preceded or accompanied by the presence of albumin and of tube-casts in the urine. Beyond the production of the symptoms spoken of, arsenic should never be pushed in medicine.

THERAPEUTICS.—When arsenic is administered in small repeated doses, it may act as a tonic, by slightly irritating the stomach and thereby provoking an appetite ; and in certain cachexias it increases the muscular strength and the general vigor. The history of arsenic-eating indicates that the drug has some positive tonic influence over nutrition ; and although the amelioration—the increase of strength and blood—by its use in cachexias may be due to an indirect action of the drug,—to a removal or overcoming of the morbific agent of the disease, and a consequent allowing of the recuperative powers of the system to assert themselves,—there is much reason for believing that it does act as a direct stimulant to nutrition. All that we know of the effect of arsenic upon the system throws only enough light on its therapeutic action to enable us to class it as an alterative,—a modifier and often an improver of nutrition.

After very much discussion * it seems to be established that many of the Styrian peasants use arsenic habitually in large quantities ; the young girls to beautify their complexions and enhance their charms ; the men with the belief that it will increase their "wind," endurance, and sexual powers. The best authorities state that the arsenic-eating is practised chiefly in the northern and northwestern parts of Styria ; that the white arsenic is preferred, the yellow commercial article being sometimes taken, the native red arsenic, or orpiment, very rarely ; that the commencing

* See Vogt (*Lehrbuch der Pharmacodynamik*, Aufl. iii. i.), Charles Heisch (*Pharm. Journ. Trans.*, 1859 and 1860, i. 556 ; *British and Foreign Med.-Chir. Review*, xxix. 144), and C. Maclagan (*Edinb. Med. Journ.*, 1864, 203 ; *Edinb. Med. and Surg. Journ.*, 1871, xvi. 569).

dose is about 0.22 grain, which is very slowly increased to 0.62 grain avoirdupois.*

Among the diseases which clinical experience demonstrates are especially benefited by the use of arsenic is *chronic malaria*. No one would at present think of employing the drug in acute *remittent fever*, or even in acute *intermittent*, unless under very peculiar circumstances. It is in those cases which have resisted quinine, in which the paroxysms have become irregular, returning at long intervals, and in which the anæmia and the general nutritive disturbance are even more prominent than the febrile disorder, that arsenic is especially valuable. In these cases it should be administered with sufficient boldness, very generally in conjunction with iron. George B. Wood recommended that the first doses should be as large as the system will endure, so as to make a decided impression at once. When the ague paroxysms are frequent, it is perhaps well to employ this plan; but when it is the cachexia rather than the active disorder that is to be combated, it is preferable to commence with small doses and to increase them until some constitutional symptom is produced. In ordinary *intermittents*, after the paroxysms have been broken up by quinine it is very well to place the patient upon a preparation of arsenic and iron, as a prophylactic against their return. When, in ordinary *intermittent* fever, for any cause quinine cannot be administered, arsenic may be employed. In these cases, as already intimated, the first doses should be large, so as to make an immediate impression; from five to ten minims of Fowler's solution, properly diluted, may be given every two or three hours until some decided symptom is produced. When the stomach refuses the remedy, it has been recommended by Boudin to give it by the rectum, which he affirms will often bear even a grain of the acid. Not more than a third of this amount should, however, be used as a commencing dose. In *malarial intermittent neuralgia*, arsenic may be employed as a very useful adjuvant to the antiperiodic alkaloids. K. M. Downie[32] calls attention to the value of arsenic as a *prophylactic* against malaria. His trials were not numerous enough to be conclusive, but so far as they go they indicate that arsenic is even superior to quinine.

It is alleged that arsenic injected directly into the growth is an effective remedy in *lymphatic tumors*, especially in the affection known as malignant *lymphoma*.†

In various *skin diseases* arsenic is a valuable remedy. Concerning its use Louis A. Duhring says, "Arsenic exerts its influence chiefly upon the epidermis. Its action is upon nutrition through the nerves. Hence it is found that diseases affecting the more superficial strata of the integument are most amenable to its influence. It is a tonic to depressed states

* Maclagan says that in one case of suspected poisoning in Styria the prisoner was acquitted on the ground that the deceased was an arsenic-eater. (See also *Wiener Klin. Wochensch.*, 1892, v.).

† See *Wien. Med. Wochenschrift*, 1871; *Arch. f. Klin. Chir.*, xviii.; *Stricker's Jahrb.*, 1877.

intense itching, or rapid cell-change. It is not only gene
benefit at this stage, but in most cases is positively injurious,
augment the activity of the morbid process. It stimulates t
layer into increased action when rest is most needed. Its adm
as a rule, should be withheld until the acute symptoms have s

"Arsenic is unquestionably of great value in *psoriasis*, but
means of benefit in every case, nor should it be prescribed f
or in all stages. Some cases are aggravated in a marked de
When the process is very active, and attended by much inf
as a rule it aggravates the disease. The more active the cell-p
the less probability is there of its being of benefit. On the
the more indolent and sluggish the disease the greater the
improvement. It should, as a rule, be withheld until the p
fairly settled in its course. In cases of long standing which m
disposition to undergo change it is particularly useful.

"Arsenic is of service in certain varieties of *eczema*, espec
chronic squamous and papular varieties and where the elemen
are ill-defined, and also where the disease is superficially seate
little infiltration in the skin. Certain forms of persistent loca
lar and vesicular eczema having a tendency to recur, as, for
the fingers, also often yield to it. It should be avoided in ac
unless the case is distinctly neurotic.

"*Pemphigus* is generally favorably influenced and often
cured by its use. It should be prescribed cautiously but fearl
doses usually being called for. It is the most reliable reme
disease. In *lichen* it is usually employed with great advantage
in *lichen planus*, in the rare *lichen ruber* of Hebra, and in allie
Occasionally it may be given with benefit in chronic *urticaria*.

"It may prove of value in certain cases of *acne* and *comedo*

or so-called *fibroid phthisis*, but even in true *tubercular phthisis* when the course is very slow and chronic. In *asthma* it may be given internally and also used locally. (See EXPECTORANTS.)

In certain nervous diseases arsenic acts very favorably, in some unknown way. In *chorea* it has acquired a deserved reputation. In this affection iron and other tonics are generally indicated and may be given consentaneously with the arsenic. It is best, however, to administer the latter separately, as the dose must steadily be increased until œdema or other manifestations betray a decided action. Arsenic has from time to time been strongly recommended in *whooping-cough*, *non-malarial neuralgia*, and simple *gastralgia*, or *gastric neuralgia*.

Arsenic is of value in those forms of *chronic rheumatism* in which potassium iodide is commonly employed. It is often advantageous to alternate, administering one of these alteratives for three or four weeks, and then the other for the same length of time. In *rheumatic gout*, or *rheumatoid arthritis*, it has been highly extolled.

TOXICOLOGY.—The symptoms of acute arsenical poisoning resemble so closely those of cholera nostras that without the knowledge of the taking of the poison, or chemical analysis of the excretions, a positive diagnosis may be impossible. The abdominal pain is, however, usually more severe than in the natural disease.

Chronic arsenical poisoning is often of difficult diagnosis. The symptoms are usually local and constitutional. Irritation of the respiratory mucous membrane may be shown by dryness of the throat, cough, respiratory disturbance, and other evidences of chronic bronchitis or of severe laryngo-bronchial catarrh, whilst loss of appetite, nausea, colicky pains, intestinal irritability, mucous discharges, or more marked signs of intestinal catarrh may be intermingled with weakness, depression of spirits, irritability, insomnia, giddiness, tinnitus aurium, failure of memory, or other symptoms of cerebral or general neurasthenia. The disturbance of nutrition may be evidenced not only by emaciation or by especial muscular wasting, but also by pronounced swelling of the small joints, and a peculiar brown pigmentation of the skin which is almost pathognomonic of chronic arsenicalism. The discoloration may be localized or wide-spread, confined to the trunk or to the extremities of the body, or may even cover almost the whole surface. There may be muscular tremors or stiffness ; vertigo or other disorders of equilibration are sometimes seen, whilst violent neuralgic pains, with numbness of the extremities, marked tenderness of the nerve-trunks, and other results of peripheral neuritis, are not rare. In most cases of chronic arsenical poisoning without a history the congeries of symptoms is, however, sufficient only to arouse suspicion and to call for a chemical examination of the urine. It should always be remembered that a peripheral neuritis is usually due to the presence of some poison, and that a group of wide-spread atypical symptoms not characteristic of any distinct disease is usually either toxic or diathetic.

Sometimes in acute, more frequently in chronic, arsenical poisoning, or as the result of long-continued medicinal use of the drug, certain disorders of the skin appear.* Of these, herpes zoster seems to be the most frequent; it probably is the result of an arsenical neuritis. There have been observed, as produced by arsenic, wide-spread deposit of pigment in the skin and mucous membranes, constituting almost a true melanosis, erythematous and desquamatous eruptions, urticaria and subcutaneous œdema, vesicular eruptions, bullæ, papules, pustules and ulcers, purpura, shedding of the hair and nails, and keratosis.

In artisans who work in copper local arsenical poisoning is not very rare. Ulcers about the roots of the nails are generally the first trouble in these cases, but after a time eczematous or papular eruptions appear, and even subdermal erysipelatous inflammation is developed. Very commonly to these local symptoms are added, after a time, the usual phenomena of chronic arsenical poisoning.

In the arts, preparations of arsenic are largely used as pigments; and, excepting the manufacturers of arsenical compounds, it is almost exclusively those who are accidentally exposed to the deleterious influence of these pigments that suffer from chronic arsenical poisoning.

The poisonous colors are of various hues, and, being very cheap, and remarkable for their purity of tone and their permanence under exposure to light, are much used by paper-makers. *Scheele's Green*—copper arsenite—contains fifty-five per cent., by weight, of arsenous acid; and *Schweinfurt Green*—the aceto-arsenite—fifty-eight per cent. Paper coated with them has been largely used not only for hangings, but even as wrappings for confectionery and other edibles. The arsenical dyes are not all green, but may be in almost any hue; they are largely due to the use of arsenic in the manufacture of magenta and other aniline colors. E. S. Wood,[33] of Harvard, has shown that in different parcels of the same goods one will contain arsenic and the other not, because the aniline dyes are sometimes contaminated with arsenic and are sometimes free from it. These poisonous colors are by no means confined to wall-paper. Sweetmeats have been colored with them; pasteboard boxes, artificial flowers, tarlatan dresses, India muslins, cretonnes, walls of dwellings, shelves of groceries, toys of children, and various other articles have been made the vehicles of death, so that hundreds of cases of poisoning have

* See *Berlin. Centralblatt*, 1868; *Deutsche Klinik*, 1874; *Schmidt's Jahrb.*, clxv, 1; *Deutsch. Archiv Klin. Med.*, 1899, xliv.; *Boston Med. and Surg. Journ.*, cxviii., cxix., cxx., cxxi., cxxii.; *Berlin Thesis*, 1892; *Ann. Dermat. et Syph.*, iv.; *Vierteljahr. Derne.*, Wien, 1897, xi.; *Ann. de Dermatol. et de Syph.*, 1897, viii. 4, 345; *Monats. Prakt. Dermatol.*, 1897, xxiv. 3, 137.

† For an excellent report upon this subject, see *Report of the State Board of Health of Massachusetts*, Jan. 1872, where it is stated that from five hundred to seven hundred tons of arsenical pigment were manufactured in 1862 in England alone. Fatal chronic arsenical poisoning from working in aniline dyes is reported in *Stricker's Jahrb.*, 187, 501. F. C. Shattuck (*Med. News*, 1893, lxii.) reports a number of cases in which the symptoms have been gastro-intestinal irritation, anæmia, dermatitis, redness of the conjunctiva, puffiness under the eyes, headache, irritation of the upper air-passages, albuminuria with casts and blood, and peripheral neuritis. The number of cases of chronic arsenical poisoning detected in and about Boston, contrasted with the rest of the world, is something remarkable, and is scarcely to be accounted for by the alleged superior acuteness of the Boston physicians. A further difficulty of the subject is that arsenic has been detected in the urine of many normal Bostonians.

resulted from the use of these pigments, which ought to be banished by the strictest laws. In most cases it is probably the minute dust, which is separated mechanically and diffused through the room, that produces the fatal result; but poisoning has occurred when the arsenical paper was covered over with another paper. Hambers has made elaborate chemical researches upon the air of these apartments, and believes that he has demonstrated that some arsenic escapes in the form of arseniuretted hydrogen. Not rarely the poison has been taken directly into the stomach, especially by children.

Arsenical Poisoning.—Death usually results in from eighteen hours to three days; but Taylor reports a case in which it occurred with tetanic symptoms in twenty minutes, and life has been protracted until the sixteenth or even the twentieth day. The effects of the arsenical solutions, such as Fowler's, are more rapid and severe than those of the solid drug. Tardieu places the minimum lethal dose at from ten to fifteen centigrammes (1.54–2.31 grains).

W. C. Jackson[34] records a case of recovery, under the early use of emetics, after an estimated dose of two ounces had been taken; and E. D. Mackenzie[35] gives an account of a man who swallowed an unknown quantity of arsenic in lumps, and received no treatment for sixteen hours, yet recovered after passing per anum one hundred and five grains of arsenic in two masses. On the other hand, death has resulted from the use of very small amounts. Taylor asserts that the smallest fatal dose hitherto recorded is two grains. Lachèse[36] affirms that six milligrammes (0.09 grain) will produce decided but not serious symptoms, and that from one to three centigrammes (0.154–0.462 grain) are poisonous, and from five to ten centigrammes (0.77–1.54 grain) fatal. The escapes from death after the ingestion of large amounts of arsenic have, without doubt, depended upon its being, as in the cases above narrated, in an insoluble form.

TREATMENT.—As arsenic in large doses generally induces vomiting, it is rarely necessary in poisoning to evacuate the stomach by artificial means. If free emesis, however, have not occurred, a prompt emetic, such as mustard or zinc sulphate, should be at once exhibited, and very generally the stomach should be well washed out by large draughts of warm water, with salt, if necessary for the return of the water. With the emetic, or sooner, if possible, the antidote should be administered. The most certain antidote is the *freshly precipitated ferric hydrate*, which forms with arsenous acid a very insoluble compound. The antidote must be freshly prepared, and must be given in great excess; according to the experiments of T. and H. Smith, of Edinburgh, at least eight grains of the iron being required for the conversion of one grain of the arsenous acid.

In practice, any of the official ferric solutions—that of the chloride being generally preferred, as most readily procured—should be neutralized by sodium carbonate or preferably by magnesia, and a portion of the precipitate given at once, stirred up in *hot* water. The remainder of the antidote, having been hastily washed by emptying it on to a piece of muslin or a filter, pouring water on it and allowing it to drain, should be administered very freely, indeed indefinitely, as it is entirely harmless. H. Köhler,[37] of Halle, has made an elaborate series of chemical,

physiological, and clinical experiments upon the comparative antidotal values of the *saccharated* ferric oxide and the freshly precipitated ferric hydrate. His results indicate that the former preparation is the better; but, as the efficiency of the hydrate has been so frequently proved at the bedside, further testimony is desirable before it is superseded, especially since the other ferric preparation is not official with us, and is not so readily prepared on the spur of the moment as its fellow. *Dialyzed iron* has been used with very good results, but it is much better to precipitate it, just before administration, with a small amount of ammonia or other alkali. *Magnesia*, freshly calcined or freshly precipitated from a solution of its salts, is an antidote of some avail in arsenical poisoning, but is decidedly less efficient than the iron oxide.

The best form of the antidote is probably FERRI OXIDUM HYDRATUM CUM MAGNESIA, U. S., *Arsenical Antidote* of the German Pharmacopœia. It is made by precipitating the solution of ferric sulphate by magnesia, and is probably the best of the antidotes. In emergencies, Monsel's solution, tincture of the ferric chloride of iron, or other of the ferric preparations may be substituted for the tersulphate.

In arsenical poisoning castor oil should be administered for the purpose of expelling the poison from the bowels, and demulcent drinks, opium, stimulants, dry external heat, and rubbing should be employed as called for by the symptoms. When there is a tendency to suppression of urine, very large draughts of feebly alkaline water should be given as frequently as the stomach will bear.

The chief indications in *chronic arsenical poisoning* are to remove the patient from the exposure and to treat symptoms as they arise.

ADMINISTRATION.—The beginning dose of arsenic is one-thirtieth of a grain (0.002 Gm.), which should be given in pill *after* meals, and be slowly increased until a perceptible influence, or the desired therapeutic effect, is obtained. In many cases (*chorea*, *lymphoma*, *intermittent fevers*, etc.) it is necessary to push the remedy until decided evidences of poisoning are secured: in this case a liquid preparation should be selected. The following are the official preparations of arsenic:

LIQUOR POTASSII ARSENITIS. U. S.—*Fowler's Solution* (arsenous acid four and a half grains to one fluidounce) is nearly colorless and odorless, with a faint taste of the compound spirit of lavender, which is in it. Dose, five drops (0.3 C.c.) in a wineglassful of water after meals, to be increased and used with the same precautions as arsenic.

SODII ARSENAS. U. S.—*Sodium Arsenate* occurs in transparent, slightly efflorescent, soluble crystals, and is solely used in making the LIQUOR SODII ARSENATIS, U. S. *Solution of Sodium Arsenate* (about four and a half grains to one fluidounce) is equivalent to Fowler's Solution.

LIQUOR ACIDI ARSENOSI. U. S.—*Solution of Arsenous Acid* is in strength and theraputic use equivalent to Fowler's Solution.

ARSENI IODIDUM. U. S.—*Arsenic Iodide*.—This is an orange-red, crystalline solid, wholly soluble in water and entirely volatilized by heat. It has been used as an alterative, and also as an external application in *lupus* and *chronic tubercular affections*.

HYDRARGYRUM—MERCURY. U.S.

Local Action.—The local effect of mercurial preparations varies from complete inertness to an active escharotic influence, so that each preparation must in this regard be studied by itself.

Absorption and Elimination.—All preparations of mercury yield themselves or the mercury in them to absorption, and after absorption to elimination. The metal has been found in the blood,* in the urine, in the serum of ulcers, in the saliva, in the fæces, in the pus from ulcers, in the seminal fluid, in the milk of nursing women,—indeed, in every conceivable secretion and in every tissue. Heller found it in the aborted fœtuses of salivated women, and Mayençon and Bergeret in the urine of a baby whose nurse was taking calomel; and each of these observations has been confirmed by Wellander.

An enormous amount of work has been done to determine how rapidly mercury is eliminated, and whether when given internally it is all thrown out of the system. The result of all this labor seems to us to prove that the single dose of mercury does not remain in the system, but that when the drug is administered constantly for a length of time elimination does not keep pace with absorption, so that the mercury accumulates in the tissues. Moreover, the elimination takes place irregularly and intermittently, for reasons that at present cannot be made out. Further, there does not appear to be any limit of time during which stored-up mercury may remain in the body; indeed, all the probabilities point to the possibility of mercury being deposited in the tissues in such form that it is practically inert and exerts no effect upon the system; liable, however, under certain agencies, to be set free and to exert its power upon the general nutrition.†

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* Eld and Buchner (quoted by Stillé); Cantu, Jourda, Andouard (quoted by Stillé); Fourcroy (quoted by Stillé); Gmelin (*Bull. de Thérap.*, xiii.); Byanon (quoted by Mayençon and Bergeret); Salkowsky (*Virchow's Archiv*, xxxvii. 347); Oesterlen (quoted by Stillé); Salkowsky (*loc. cit.*, 347); Mayençon and Bergeret (Robin's *Journal de l'Anatomie*, 1873); Klinik (*Detroit Med. Journ.*, May, 1877).

† The rate of absorption of mercury is of course affected by the choice of preparation and by the method of administration. Wellander (*Ann. Dermatolog.*, vii. 413) has found mercury in the urine fourteen hours after its application to the human skin and one hour after its subcutaneous administration. Mayençon and Bergeret found that when one centigramme of corrosive sublimate was given hypodermically to a dog, the urine for the next twenty-four hours contained mercury, afterwards none. When a centigramme was given daily for ten or twelve days, the urine contained mercury for four or five days after the cessation of medication. In their last series of experiments, rabbits received the drug, and were killed at different intervals: in half an hour the metal could be found in all the tissues, the liver and kidneys containing most of it; in four days, or even in a shorter time, mercury given in a single dose was all eliminated, and could not be found in the tissues.

The evidence in favor of the storing up of mercury in the system is overwhelming. In 1880 Vajda and Paschkis (*Ueber den Einfluss Quecksilbers*, Wien) stated that they found the metal in the urine in different cases, six months, one year, two years, and even twelve and thirteen years after the mercurial course. Mayençon and Bergeret found that the exhibition of potassium iodide forty-eight hours after the cessation of a mercurial course, when the urine was free from mercury, would bring about the immediate elimina-

PHYSIOLOGICAL ACTION.—When a mild, unirritating preparation of mercury is introduced into the system so as to produce constitutional effects, the first symptoms of its action are to be looked for in the mouth. In the mildest degree these symptoms consist of a slight fetor of the breath, and some soreness of the teeth when knocked forcibly together or struck with a key. Mercurial fetor of the breath is generally the first indication that the drug is affecting the system, and is sooner or later accompanied by a disagreeable metallic taste. If the use of the mercury be persisted in, the gums become swollen, soft, and spongy, bleeding on very slight abrasion, and there is a decided increase in the secretion of saliva. Beyond this point the therapeutist is never justified in carrying the use of the drug. If it be done, the local symptoms in the mouth increase in severity, the tumefied gums become inflamed, very vascular, and marked by a dark red line at the junction of the teeth; the tongue is also swollen, sometimes enormously, protruding from the mouth, whose closure it may entirely prevent; the teeth are loosened in their sockets; the saliva is enormously increased in quantity and altered in quality, forming great, ropy, viscid masses, which pour over the thickened lips; the parotid glands, and even the submaxillary, are very much enlarged and tender. Sometimes, before salivation occurs, slight systemic erethism, marked by a quickened pulse and general restlessness, may be present; but when the mouth-symptoms are severe, very generally there is a distinct febrile reaction of a low type.

In some cases of mercurialization the stomatitis has been very intense, loss of the teeth, extensive ulceration of the soft parts, and even necrosis of the jaw-bones have occurred, and death from exhaustion resulted, or the patient struggled through to recovery, seamed and disfigured for life. In these cases passive hemorrhages often recur again and again,

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tion of mercury. Sigismund has detected quicksilver in the urine of patients as long as thirteen years after taking the medicine; but Schuster (*Zeitschr. f. Klin. Med.*, 1884, vii.) asserts that these patients were habitués of a room in which inunctions were constantly being made, and that under these circumstances there is sufficient diffusion of the mercury to produce a very sensible effect in those breathing the air. Apparently, however, using all precaution and having the patient carefully watched, H Stein (*Wiener Klin. Wochens.*, 1890) has obtained weighable amounts of eliminated quicksilver from the urine four weeks after its inunction. (See also *Viertelj. f. Dermat. u. Syphilis*, 1882; *Annales de Dermat. et Syphil.*, 1882, iii.) Schuster has found it in the fæces three months after the cessation of a mercurial course (*Viertelj. f. Dermat. u. Syphilis*, ix. 307); indeed, he believes that it is thrown off more freely and constantly by the intestines than by the kidneys. He also asserts that elimination is completed six months after the cessation of an ordinary mercurial course (*Journ. of Cutan. Med.*, i. No. 12, ii. No. 9). In an elaborate memoir on the elimination of mercury, Balzer and Klumpke (*Revue de Médecine*, 1888, viii.) state that extraordinary exacerbations and remissions occur in the elimination during treatment, that Michaelowsky and Souchow have shown that the effect of potassium iodide is small, but that Stepanow has proved that the hot-air baths increase enormously the elimination. It appears to be established that in these cases of long continuance the mercury escapes not only through the kidneys, but is also excreted by the salivary glands as well as by the intestines, and hence its continuing elimination may be overlooked by the chemist, who simply studies the urine. (See paper by Stein and Kronfeld, *Wiener Med. Wochen.*, 1890.)

and may contribute largely to a fatal result. During severe ptyalism emaciation goes on rapidly, and seems to affect especially imperfectly organized tissues, so that exudations very generally rapidly disappear. The disturbance of nutrition is further shown in some cases by the occurrence of ulcers upon the extremities. The blood suffers very decidedly, becoming more fluid and watery than normal and having its power of coagulation impaired. According to the researches of Wright, its solid constituents are notably diminished, including albumin, fibrin, and the red corpuscles, and it contains a large quantity of a fetid, fatty material. These observations of Wright have been confirmed upon animals by Wilbouchewitch,[1] and by I. Hughes Bennett.

Although large doses of mercury lower the general nutrition and destroy the crasis of the blood, it is probable that given in very minute doses it has tonic properties.

In 1869 Liégeois[2] asserted that the subcutaneous injection of very minute doses of quicksilver produces in healthy men an increase of their bodily weight, and in 1876, in two experiments, E. L. Keyes[3] found that not only was the bodily weight increased, but, as determined by actual count, the number of the red corpuscles was decidedly augmented. Recently Hermann Schlesinger[4] has laboriously experimented upon rabbits and dogs. All other conditions being similar, those rabbits which received the mercury increased in weight a very little more than did those to which mercury was not given, but the augmentation of the red blood-disks was distinctly greater in the mercurialized animals. With dogs the results were more decided, both bodily weight and blood-corpuscles increasing much faster in the animals to which mercury was given. I. Hughes Bennett had previously obtained results similar to those quoted, and Schlesinger thinks that it must be considered proved that very minute continuous doses of mercurials tend in the normal animal or man to increase distinctly the weight of the body and the richness of the blood, but that it is scarcely proper to call them tonic, as in his belief they act by hindering oxidation and restricting waste, and not by aiding in reconstruction,—a conclusion which is purely theoretic and unproved. In some cases of syphilitic anæmia the effect of mercury in increasing the number of red blood-corpuscles is very marked. This effect is, however, to be attributed to the antisyphilitic influence of the remedy rather than to any specific action on the blood-making organs. (For elaborate paper, see L. Gaillard.[5])

The ordinary symptoms of mercurialization have been sufficiently described, but there are on record various anomalous cases. In some instances the chief symptoms of mercurialism have been cutaneous.

The usual eruption is a polymorphic erythema, resembling more or less that of scarlet fever. In rarer cases the eruption may be distinctly erysipelatous, with subdermal œdematous swelling. Sometimes it takes the form of urticaria, or even of a roseola; a very severe eczema, becoming finally pustular, has in some cases been produced, most frequently as the result of an inunction ; whilst mercurial pemphigus and purpura have both been recorded. Usually the eruption is fugacious, being followed in two or three days by more or less desquamation, but very grave cases have been recorded in which there has been a universal dermatitis, with great swelling of the face and extremities, excessive desquamation, followed by thickening and infiltration of the subdermal tissues, excoriation, violent fever, disturbance of the respi-

ration, and death; or, if the patient survive, months of illness (see M. A. Morel-Lavallée.[6]

Sometimes the influence of mercury falls almost exclusively upon the nervous system, and produces a peculiar train of paralytic phenomena.

Nervous mercurialism occurs chiefly when mercurial vapors find entrance through the lungs, and is most frequently seen in workers in the metal. It is generally the result of long exposure; but that it may be produced in a very short time is proved by the case, related by Christison, of two barometer-makers who slept one night in a room containing a pot of mercury upon a stove. One was severely salivated, the other was affected with a shaking palsy which lasted all his life. According to Sigmond,[7] the attack of mercurial palsy, which is sometimes sudden, sometimes gradual, begins with unsteadiness and shaking of the extremities and of the muscles of the face, which movements interfere with walking, speaking, or chewing; the tremors become frequent, nay, almost constant; "every action is performed by starts." If the exposure be continued, sleeplessness, loss of memory, and death terminate the scene. A peculiar brownish hue of the whole body, and dry skin, generally accompany the disease. In its first attack it may be mistaken for St. Vitus's dance; in its latter stages, for delirium tremens. According to Nöel Guéneau de Mussy,[8] these two forms are distinct varieties rather than different stages of mercurial tremors. In the latter the affection simulates *paralysis agitans* in its shaking movements; in the former the motions are violent, and occur independently of the will of the patient, even when he is lying quietly in bed. In a case reported by L. Langer,[9] the electro-contractility of the affected muscles was much heightened.

Paralysis from chronic mercurial poisoning is said to be not a rare affection among artisans and miners who are in their daily occupation exposed to contact with the metal or its fumes. The subject has been thoroughly discussed by M. M. Letulle,[10] to whose paper the reader is referred for a collection of recorded cases and for details. In a case reported by Sigmond, symptoms similar to those of chronic lead-poisoning, including wrist-drop, followed repeated mercurial inunctions. In some cases mercurial paralysis takes the form of multiple palsy, or of a brachial or crural monoplegia, or of an obscure local palsy, as in a case reported by Küssmaul, in which there was aphonia from paralysis of the laryngeal muscles. Almost invariably the loss of motor power is accompanied by an anæsthesia, which may be wide-spread or may be in isolated islets, or may take the form of hemianæsthesia. The loss of sensation is very rarely absolute; simple loss of the thermic sensibility or analgesia may exist alone. Partial anosmia or amblyopia may show that the nerves of special sensation are affected. Neuralgic pains may be the permanent result of a mercurial exposure, and epilepsy and even insanity, most frequently of the melancholic type, are stated to have been so produced. According to Letulle, trophic changes are not common, the paralyzed muscles not undergoing atrophy, and retaining their normal relations to the galvanic and faradic currents. When the thighs are affected the knee-jerk may entirely disappear. Guinon[11] describes violent hysteria following upon chronic mercurial intoxication.

In some cases exposure to the vapor of mercury, or even its persistent medicinal use, has resulted in the production of a state of the system somewhat resembling scurvy, characterized by great anæmia, emaciation, and general loss of power, with loss of the hair, aching pains in the bones and joints, œdema, fetid breath, diarrhœa, and generally disordered secretions. This is the so-called *mercurial cachexia*.*

* For an interesting paper in regard to mercurialism in looking-glass makers, see article by Wollner (*Münch. Med. Wochen.*, July, 1892).

There is some reason for believing that the pancreas is especially affected by mercury. Thus, in a case related by Copland, a woman after excessive salivation experienced deep-seated epigastric pain and heat, with nausea, thirst, and fever, and voided thin stools containing liquid resembling salivary fluid. At the post-mortem the pancreas was found weighing four ounces, red, congested, and with its duct dilated. In regard to the action of mercury upon the liver, see PURGATIVES.

The experiments of I. Brauer[12] and of V. Tirelli[13] show that in the lower animals very large doses of mercurials have a powerful depressing influence upon the central nervous system, and may produce death by respiratory paralysis ; that when smaller doses are given a condition of nervous excitement is produced, with increase of the tendon-reflexes, followed by partial paralysis and ataxia ; and that in chronic poisoning by very small doses continuously administered a degeneration of the nervous system takes place, probably beginning in the anterior motor cells of the spinal cord. This degeneration appears, however, not to be characteristic of the mercurial poisoning, but to be similar to that produced by phosphorus, arsenic, and various other poisons.

Little attention has been paid to *local mercurial* poisoning, but A. W. Foot[14] has reported the production of paralysis of the muscles of the hand and forearm by contact with the red mercury iodide during the rubbing of cattle with a salve containing it. It is asserted that in some peculiar persons the external, and even the internal, use of small amounts of mercurials will produce violent eczema or other skin-eruptions (Alexander[15]).

The constitutional action of mercury shows that it has relations to the nutrition of the whole body. The alterations in the blood, the wasting, the perverted functions of nerves and of glandular tissues, the various skin eruptions, all point to a profound influence upon the whole organism. After death from such irritant preparations of mercury as corrosive sublimate, violent diphtheritic colitis is the ordinary lesion, and, as was first shown by Salkowsky, structural alterations abound in the kidneys, accompanied by a peculiar deposit of calcium phosphate : that the renal lesions may be produced by the non-irritant preparations of mercury has been shown by B. Silva,[16] who has found true desquamative nephritis in dogs to which calomel had been given. Felix Klemperer[17] discusses the literature of the subject fully, and concludes that the successive changes in the kidneys are : excessive hyperæmia, parenchymatous nephritis, hemorrhagic nephritis, with wide-spread degeneration of the epithelium, and in about one-half of the cases deposits of chalky material. Virchow[18] states that the coexistence of distinct renal chalky deposits with diphtheritic hemorrhagic colitis justifies the diagnosis of corrosive sublimate poisoning, but Klemperer affirms that this condition can be produced by bismuth and some other poisons. The later researches of E. Lentert[19] led to a similar conclusion,—namely, that the calcification of the kidneys makes the diagnosis of corrosive sublimate poisoning very probable but not assured. The calcification of the kid-

neys, which is often accompanied by true calcareous deposit in the tubules, and which may be sufficient to cause the kidney structure to cry out under the scalpel, was attributed by Prevost [20] to the decalcification of the bones; a theory which seems to have been disproved by Klemperer (confirmed by Paul Binet [21]).

According to our present evidence, it does not seem probable that mercury increases the nitrogenous waste. It is true that Hermann von Boeck,[22] in a case of mercurialization in a man, found that there was a very slight increase in the elimination of nitrogen during the mercurial periods, but H. Schröder,[23] and Guttenberg and A. Gurber,[24] in experiments made upon rabbits, obtained an absolute decrease in nitrogenous elimination during mercurial poisonings.

THERAPEUTICS.—The use of mercury in affections of the liver and of the alimentary canal is fully discussed in another portion of this treatise; and, although the drug has been used for almost innumerable purposes in times past, it seems here only necessary to speak of its action as an antiphlogistic and as an antisyphilitic.

Antiphlogistic Action.—The use of mercury in inflammation originated towards the close of the last century with Robert Hamilton, and soon became universal in England and America. It is a matter of regret that no sufficient analyses of the blood of ptyalized persons have been made to determine exactly what are the changes produced in the vital fluid by mercury. The indications are, however, very strong that chief among them is a lessening of the amount of fibrin. As is well known, increase of the hæmic fibrin is one of the most characteristic effects of inflammation: consequently, theory, instead of being opposed to the antiphlogistic use of calomel, affords at least some grounds for the belief that there is more or less antagonism between the processes of mercurialization and of inflammation.

All important evidence as to the antiphlogistic value of mercurials at present available is clinical, and even of this it seems impossible to find much that is very exact and of such nature as to exclude possible fallacies. It is the enormous mass of testimony that overrides the probability of fallacy. It is the general judgment of the profession, founded upon the thousand daily observed bedside facts, that endorses the use of mercury as an antiphlogistic. In other words, our knowledge of the value of mercurials in inflammation at present is clinical rather than experimental, empirical rather than scientific, but it seems scarcely possible that it is not correct. There is one inflammatory affection—*iritis*—which, from its anatomical relations, is completely visible at all stages; and the effects of the drug upon its processes have been noted from day to day hundreds of times. Oculists are, we believe, agreed that when there is a marked tendency towards the exudation of lymph in this disease, mercury should be exhibited until ptyalism is induced.

Of all inflammations, those of the *serous membranes* seem to be most allied to iritis; and it is exactly in the condition above spoken of, where

there is a tendency to fibrinous exudations in *pleuritis*, *peritonitis*, and *pericarditis*, that mercury is so constantly employed with so good an effect. In parenchymatous inflammations, especially in *pneumonia* and in *hepatitis*, mercury has been used with asserted advantage by many practitioners, but its value is certainly more questionable than in serous inflammations. In *pseudo-membranous angina* or *laryngitis*, and in true *diphtheria*, the mercurials are very useful remedies; they should be given in small repeated doses, preferably in the form of dry calomel powders, it being probable that the good effect is at least in part due to the diffusion of the mercurial over the diseased surface and the consequent antiseptic influence. There is much doubt as to the exact advantageousness of mercurials in *endocarditis;* but, as it is extremely important, if possible, in that disease, to prevent exudation, and as mercury is the most efficient known agent for effecting this, it should be administered freely and at once.

In whatever disease a mercurial is administered as an antiphlogistic, it should be given during the stage of exudation, and to facilitate the absorption of the newly organized lymph after it has ceased to be thrown out. In the majority of cases mercury given for its constitutional effects should be combined with opium, to prevent its acting on the bowels.

Calomel should not be used in *adynamic inflammations*, or where the exudation is serous rather than fibrinous. In *puerperal peritonitis* it has been strongly advocated by some and as strongly condemned by others, simply because there are two varieties of the disease, the *sporadic* or *sthenic*, and the *epidemic* or *asthenic;* and in the one both bleeding and calomel are strongly indicated, while in the other they are effective only for evil.

Mercury as an Antisyphilitic.—The literature concerning the use of mercury in the treatment of syphilis is so enormous as almost to defy analysis; through the discussion, however, has finally been reached practical unanimity of professional opinion, the only points of difference being as to details of "how" and "when" the mercury should be employed.

Whenever a venereal ulcer offers the characteristics of a true chancre, mercury should be exhibited. Many practitioners believe that it is wiser for diagnostic purposes, in all cases of doubt as to the character of the primary sore, to withhold the mercury until secondary manifestations appear. Under any circumstances, so soon as the diagnosis of syphilis is clearly established, mercury should be employed in some form or other. Our own practice is in the beginning of the treatment to push the mercury to the point of mild ptyalism,—*i.e.*, to the production of slight evidences of constitutional drug action,—and then to continue the medicine persistently in small doses for at least eighteen months, increasing the dose up to mild ptyalism if at any time there should be a recrudescence of the symptoms.

In *tertiary* syphilis mercury is to be used cautiously. It is not, how-

ever, the mere length of time that has elapsed since the infection, but the condition of the patient, that guides the judicious practitioner. So long as there is no decided cachexia, if the patient has not recently been through a mercurial course, mercury should be freely used when the local lesion threatens to kill directly or to produce organic changes in a vital organ. Thus, a gumma in the heart-wall, in the upper spinal cord, or in some vital brain-region may imperatively demand active mercurialization. We have twice seen a patient slowly recovering from brain-syphilis under the influence of the iodides die by the accident of an epileptic arrest of respiration. In these cases the more rapid resolution of the gummatous masses by mercury, had that drug been exhibited, would in all probability have prevented the fatal fit. In *hereditary* syphilis a prompt mercurial impression offers the best chance of relief. At any stage of syphilis some caution and judgment should be used in the administration of mercury. As was shown by Keyes, the small dose of mercury in infected patients frequently acts distinctly in increasing the number of red blood-disks. Wilbouchewitch found that the mercurial when first exhibited increased the number of red blood-corpuscles in syphilitic patients, but after a time appeared to produce anæmia. Whatever preparation be employed, it should be so administered as to cause only signs of the constitutional action in the mouth. It is never necessary to ptyalize the patient severely. There are various methods by which this may be done. That most frequently employed, because most convenient, is the administration of small doses of calomel or blue pill by the mouth : from one-fourth to one-half grain of calomel, or twice as much of the blue mass, combined, if necessary, with opium, to prevent its action upon the bowels, may be given three times a day, and increased if required. Instead of the internal use of the mercurial, the system may be brought under its influence by inunctions.

In practising inunctions it is essential to remember that when mercury is applied to a hairy surface it is very prone to cause a troublesome irritation, due to inflammation about the hair-follicles. Indeed, the continuous application of the mercurial to almost any surface of the body will cause finally an eczematous eruption. Further, when the skin is in thoroughly good condition it absorbs much better than when it is irritated. The frequent use of the hot baths seems also to aid in the absorption, and possibly also in the elimination of the mercury ; and the good effects obtained at the Arkansas and other thermal springs largely depend upon the frequent employment of the hot bath with the free use of the mercurial. It is therefore usually better to have the inunction practised in the evening, after the patient has had a prolonged bath ; and in cases of great urgency the baths may be repeated two or three times a day, so as to produce free sweating, and the inunction practised, it may be, twice a day. In order to avoid irritation of the skin, a regular order should be maintained in the application, as follows : *first day*, inner side of both upper arms ; *second day*, inner side of both thighs ; *third day*, inner side

of both forearms ; *fourth day*, inner side of both legs ; *fifth day*, upon both groins ; *sixth day*, upon the back ; *seventh day*, recommence the series.

The advantage of inunction is that the digestion is less apt to be disturbed than when the drug is exhibited by the mouth ;* the disadvantages are the greater or less publicity which it entails, the trouble which it involves, and its apparent dirtiness. In private practice it is rarely practised except in the case of infants, when the mercurial ointment is rubbed into the abdomen and armpits, or often simply smeared upon the flannel roller or binder which usually envelops the body. The mercurialization of the nurse, with the object of affecting the child, is unjustifiable, unless the nurse and the nursling are alike diseased : indeed, to allow a syphilitic child to feed at the breast of a healthy woman is a crime.

Mercury may be used hypodermically, often with great advantage, in the treatment of syphilis. The search after novelties by clinicians and chemists has led to the invention of very many new preparations and the production of a very large literature, which was summarized in previous editions of this work, and is discussed in great detail in current monographs on syphilis. As the result of much experience, however, we are confident that the whole matter can be summed up in a single sentence, —namely, that no mercurial preparation has any distinct advantage over corrosive sublimate for hypodermic administration ; and that the great mass of the proposed preparations, including all those which contain calomel, are much more dangerous than is the corrosive chloride. From one-sixteenth to one-eighth of a grain of the bichloride should be injected deeply into the muscles of the back or of the thigh daily or every other day, according to the needs of the case ; care being exercised to see that the part is well rubbed immediately after the injection, so as to dispel the local accumulation of fluid, and that injections are not given on successive days in places near to one another. In some cases very pronounced pain is produced ; this can be overcome, however, by injecting one-quarter of a grain of cocaine immediately before the injection of the mercurial into the same spot. The advantages of hypodermic medication are the rapidity and power of influence, the cleanliness, and the avoidance of gastro-intestinal irritation.

Mercury is sometimes administered in secondary syphilis in the form of fumigations. The patient is placed upon a chair, and surrounded by a large blanket or, better, india-rubber cloth, so arranged as to fit tightly

* The action of inunctions is usually very mild and tractable, but Von Sackur (*Berl. Klin. Wochensch.*, 1892, xxix.) has reported a case of death in six days, preceded by symptoms of violent irritation of the stomach, the intestines, and the kidneys, with furious gangrenous ptyalism, apparently produced by a single inunction with mercurial ointment. Ludwig, of Vienna, in an examination to determine the distribution of mercury given by inunction, found that it was most abundant in the kidneys, liver, and spleen ; then in the alimentary canal (least in the stomach and most in the large intestine). In the muscles the amounts were variable, in the cerebrum never sufficient to be weighed (*Internat. Klinisch. Rundschau*, 1892, vi.).

around his neck above, and below to encompass the chair. The mercurial preparation is placed upon a metal plate, heated by a spirit-lamp, beneath the chair, and the fumes are allowed to fill the space around the patient inside of the blanket. The heat produced generally causes the patient to sweat profusely, and in from fifteen minutes to half an hour the lamp should be withdrawn and the patient allowed to cool off, and after a time be put to bed and wrapped up in blankets, with the deposit of mercury still adhering to the skin. The fumigation may be practised every other night, or at longer intervals, and is believed by some to be especially useful in cases of secondary skin eruptions. Calomel, black oxide, and cinnabar are the preparations generally used ; care must be exercised that the patient do not breathe the fumes.

In advanced secondary and tertiary syphilis the mercurial iodides, given by the mouth, are often very useful, but the combination of the corrosive sublimate and the potassium iodide is in many cases still more efficient. Usually not more than one-twelfth of a grain of the bichloride should be exhibited, three times a day.

It appears to be established that certain disagreeable and, perchance, serious effects may be produced by mercurials when freely and continuously used in the treatment of syphilis, against which the practitioner must be on his guard. The most important of these is nephritis, with its consequent albuminuria. According to Heller,[25] the safest method of mercurialization, so far as the kidneys are concerned, is by the hypodermic employment of corrosive sublimate ; the most dangerous, probably, being the use of inunctions. A very rare complication which has been attributed to the mercury is polyneuritis, which has especially been noted after the very free use of mercurial inunctions.*

ADMINISTRATION.—The following preparations contain metallic mercury :

UNGUENTUM HYDRARGYRI. U. S.—*Blue*, or *Mercurial, Ointment* is made by triturating mercury with suet and lard until the metal is extinguished,—*i.e.*, until a portion of the mass rubbed upon a piece of paper exhibits no globules under a magnifying power of ten diameters. Mercurial ointment is soft, of a bluish color, becoming darker by age ; it contains half its weight of mercury. It is used to make a constitutional impression, and also locally as a resolvent, in cases of enlarged *indurated glands*. The oleate of mercury (OLEATUM HYDRARGYRI—twenty per cent., U. S.) is preferred by some practitioners.

EMPLASTRUM HYDRARGYRI. U. S.—*Mercurial Plaster* contains mercury, oleate of mercury, and lead plaster, and is used as a resolvent in *indurated glands*, enlarged *chronically inflamed joints*, etc.

MASSA HYDRARGYRI. U. S.—*Mass of Mercury—Blue Mass* is made by extinguishing mercury with honey and other inert substances. It

* See Leyden (*Deutsch. Med. Wochen.*, 1893, xix.) and R. von Engel (*Prager Med. Wochen.*, 1894, xix.).

contains one-third its weight of the metal, and is used for the same purpose as calomel, but is milder. Dose: purgative, five to ten grains (0.3–0.6 Gm.); alterative, one to three grains (0.06–0.18 Gm.). *Blue Pills* usually contain each three or five grains of the mass.

HYDRARGYRUM CUM CRETA. U. S.—*Mercury with Chalk.*—*Gray Powder* is made with chalk. It is a smooth, grayish powder, and is similar to blue mass in its medical properties, strength, and dose.

HYDRARGYRI CHLORIDUM MITE—MILD MERCUROUS CHLORIDE. U. S.

Calomel is a white, insoluble, tasteless and odorless, heavy powder.

PHYSIOLOGICAL ACTION.—Owing to the great insolubility of calomel, a good deal of discussion has occurred as to the way by which it finds entrance into the system.

According to the theory of Mialhe,[26] calomel is converted by the chlorides of the stomach into corrosive sublimate, and as such is absorbed. The action of calomel upon man is so different from that of corrosive sublimate as to render this theory exceedingly improbable, and, at temperatures even higher than that of the stomach, Mialhe was never able to obtain the formation of more than a sixteenth of a grain of the sublimate by the gastric juices. Further, Bucheim, Oettingen, and Winkler* affirm that this conversion does not occur at all at the temperature of the body. Jeannel[27] has confirmed this, and has suggested what seems to be the way in which calomel is absorbed. He finds that when the mercurous chloride is placed in a solution of an alkaline carbonate it is decomposed and the gray oxide precipitated. A small portion, however, of the latter is held in solution, as much as 0.02 part in fifty parts of water (by weight); and if a fatty oil be mixed with the alkaline solution a very large part of the mercury is dissolved.

It would appear certain that calomel entering the stomach and escaping unchanged into the duodenum is decomposed by the alkaline contents of the intestines and dissolved by the fatty matters usually present. It is possible that at times, when the stomach contains more than usual of chlorides and of hydrochloric acid, a very small portion of the calomel may be converted into corrosive sublimate, and also that when there is an excess of sulphuretted hydrogen in the alimentary canal a soluble sulphide may be formed.

The influence of calomel upon the system has been sufficiently discussed. It remains only to state that its freedom from all irritant properties is shown when taken internally or when used externally. Probably no single dose of it is capable, in the average man, of acting as a violent poison, since it is stated that in the Western United States it is very frequently taken in teaspoonful doses, that sixteen grains of it will act as vigorously as an ounce, and that a pound of it has been given in a case of cholera without visible effect.† It seems to us most probable that the absence of serious results from these heroic amounts is due to the alimentary canal being unable to dissolve—*i.e.*, to absorb

* Quoted by Stillé (*Therapeutics*, 2d ed., 655).

† George B. Wood's *Therapeutics*, ii. 565.

—the calomel. F. D. Lente has affirmed that given in enormous dose the drug acts as a sedative and does not produce mercurialization. For use of calomel as a diuretic and in dropsy, see DIURETICS.

ADMINISTRATION.—When it is desired to produce constitutional mercurialization, the dose of calomel is a half to one grain; as a purgative, from six to ten grains are administered, followed in six hours by Seidlitz powder, or other saline, if required; or, as is preferred by some practitioners, a quarter of a grain is given every hour until three grains are taken or purgation is induced. Minute doses (one-sixth of a grain) of calomel given every hour afford a very good method of impressing the system rapidly. When it is desired to get its constitutional influence, it is generally necessary to conjoin opium with it, to prevent purging.

HYDRARGYRI CHLORIDUM CORROSIVUM—CORROSIVE MERCURIC CHLORIDE. U.S.

Mercury Bichloride, or *Corrosive Sublimate*, occurs in the form of colorless crystals, or of white, semi-transparent, crystalline masses, of an acrid, metallic, styptic, and very persistent taste, soluble in sixteen parts of cold and in two of boiling water. It is at once distinguished from the other mercurial preparations by its color, taste, and solubility, and by its forming a yellow precipitate with lime-water.

PHYSIOLOGICAL ACTION.—Corrosive sublimate is a violent irritant, and in concentrated form caustic. When given in small repeated doses, although capable of inducing salivation, it is less apt to do so than is calomel or blue pill. In overdoses it produces symptoms of irritant poisoning of a severity proportionate to the dose. If the latter be small, the manifestations may be only some nausea, slight burning in the stomach, colicky pains in the abdomen, and diarrhœa. After large doses these symptoms are intensified. The subject first experiences a peculiar metallic, coppery taste at or shortly after swallowing the poison. If the solution be concentrated, deglutition is interfered with by a spasm of the muscles of the throat and larynx, causing a feeling of suffocation, and sometimes even the rejection of the draught. Then burning pains are experienced in the œsophagus and stomach, followed by violent vomiting, at first mucous, then bilious, and finally bloody, and by severe abdominal pain and tenderness, with profuse purging, at first serous in character, but afterwards affording only small, mucous, bloody stools, which are often voided with much straining. The breath generally becomes fetid and offensive in a very short time. In the course of two or three hours, very rarely in less than an hour, collapse occurs, with small, frequent, irregular pulse, pinched, anxious face, cold extremities, and finally death, preceded, it may be, by fainting, convulsions, and coma. The urine is very much lessened in quantity, is sometimes albuminous, or even bloody, and not rarely is suppressed. If the patient survives several days, a petechial eruption may appear, and salivation sometimes, but not always, occurs. In some cases, after the collapse there is an attempt at a febrile

reaction, which soon, however, gives place to a second and fatal prostration. When recovery occurs after severe poisoning, the convalescence is slow and protracted.

In regard to chronic poisoning with corrosive sublimate, sufficient has been said under the general heading, except that colicky pains and abdominal disturbance are more apt to occur with it than with the less irritating preparations. Arnozan[28] asserts that chronic catarrh of the excretory ducts of the pancreas is a pronounced lesion in chronic poisoning of animals. It should be looked for in man, and its presence might be of medico-legal value.

Severe purging, and even fatal poisoning, may result from a single external application of this preparation of mercury,* and in animals killed by hypodermic injections of it (see experiments of J. Rosenbach[29]), diarrhœa and other indications of gastro-intestinal irritation are prominent symptoms,—facts which indicate that the bichloride is eliminated unchanged from the alimentary canal. Dose, one-hundredth to one-eighth of a grain (0.0006–0.008 Gm.).

HYDRARGYRI IODIDUM FLAVUM.—*Yellow Mercurous Iodide*, U. S., is a greenish-yellow, odorless, and tasteless powder, insoluble in water, ether, and alcohol. Compared with the biniodide or the bichloride, it is a mild preparation, and has been used to produce constitutional impression in *syphilis*, especially when of long standing. The potassium iodide converts it into the biniodide and metallic mercury, and should, therefore, never be given in combination with it. The alterative dose is one-fourth of a grain (0.016 Gm.) three times a day, increased to a grain if necessary (0.06 Gm.).

HYDRARGYRI IODIDUM RUBRUM.—*Red Mercuric Iodide* is a scarlet-red powder, almost insoluble in water, but sparingly soluble in alcohol. It is a powerful local irritant, producing, when taken in overdoses, symptoms and results very similar to those caused by corrosive sublimate. It is much used in *tertiary syphilis* and in *syphilitic rheumatism;* also to some extent as a local application in *lupus*. It is much more active than the protiodide, and should be administered as cautiously and in the same doses as corrosive sublimate.

The U. S. Pharmacopœia also recognizes the following preparations of mercury:

The mercuric oxide occurs in two forms, the *Yellow* and the *Red Oxide* (HYDRARGYRI OXIDUM FLAVUM, HYDRARGYRI OXIDUM RU-

* See case reported by Meeres (*Lancet*, Sept. 16, 1871), in which a solution (two grains to one fluidrachm) was applied with a camel's-hair brush to the head of a child nine years old, for the cure of tinea tonsurans. The symptoms were diarrhœa, profuse salivation, and great prostration, ending in death. Washing out the vagina with a solution of corrosive sublimate, 1 part in 2000, has caused severe and even fatal poisoning. (See *Centralbl. für Gynäkol.*, 1884, No. 13, No. 17; also 1887, No. 47.)

BRUM): both are used upon *ulcers*, *chancres*, etc., for their local effects, and are stimulant and alterative when diluted, mildly escharotic when in powder.* From Hydrargyri Oxidum Flavum is made the *oleate* (OLEATUM HYDRARGYRI—twenty per cent., U. S.). The *Red Precipitate Ointment* (UNGUENTUM HYDRARGYRI OXIDI RUBRI—ten per cent., U. S.), the *Ointment of the Yellow Oxide* (UNGUENTUM HYDRARGYRI OXIDI FLAVI—ten per cent., U. S.), and the *Citrine Ointment* (UNGUENTUM HYDRARGYRI NITRATIS—seven per cent., U. S.) very generally require dilution with lard, and are much used in chronic *skin affections*, in obstinate *conjunctivitis*, in *psorophthalmia*, etc.

Turpeth Mineral, or *Yellow Mercuric Subsulphate* (HYDRARGYRI SUBSULPHAS FLAVUS, U. S.), a lemon-yellow powder, sparingly soluble in water, is a compound of uncertain composition, which was at one time used as an emetic in *croup*. It is, however, a very dangerous remedy, since, if it fail to vomit, it may cause a fatal gastro-enteritis, especially in the young child. Two cases of such character are recorded by A. McPhedran.[30] Forty grains[31] have caused death in the adult; profuse salivation came on in six hours. Dose as an alterative, a quarter to half a grain (0.016–0.032 Gm.); as an emetic, for a child two years old, two grains (0.13 Gm.), repeated in fifteen minutes, if necessary.

White Precipitate, or *Ammoniated Mercury* (HYDRARGYRUM AMMONIATUM, U. S.), is a white complex powder, made by precipitating the bichloride with water of ammonia. It is used in the form of ointment (UNGUENTUM HYDRARGYRI AMMONIATI—ten per cent., U. S.) as a local application in various skin affections.

Black Wash and *Yellow Wash*, two non-official but favorite preparations, are respectively made by the addition of a drachm of calomel to a pint of lime-water, and of half a drachm of corrosive sublimate to a pint of lime-water. They depend for their virtues upon the black and yellow oxides of mercury, and are used exclusively as local applications to *chancres* and other *syphilitic ulcers*. The yellow wash is much the more stimulating of the two.

AURI ET SODII CHLORIDUM. U. S.—GOLD AND SODIUM CHLORIDE.

This salt of gold, which may be obtained in large, golden-yellow prismatic crystals, is, according to the requirements of the U. S. Pharmacopœia, a slightly deliquescent powder, having an odorless but a saline and metallic taste. It is freely soluble in water.

PHYSIOLOGICAL ACTION.—The precise action of the preparations of gold upon the animal organism is not understood, but it is probable that the soluble preparations are mostly irritant poisons, whilst the insoluble preparations are either not poisonous or else act slowly upon the general system. It is stated that gold and sodium chloride, in overdose, pro-

* For severe poisoning by yellow oxide, see *Brit. Med. Journ.*, Sept. 1889.

duces pain, inflammation, and even ulceration of the stomach and bowels, and otherwise acts as a corrosive poison. It is affirmed that the gold preparations, in moderate doses, cause increased fulness and frequency of the pulse, and augment the urine and insensible perspiration, without interfering with the appetite or the regular action of the bowels; but that, if the dose be pushed too far, general irritation is apt to be produced, and inflammation to seize upon some organ, according to the predisposition of the individual, and fever is developed.

THERAPEUTICS.—Although gold and sodium chloride has been largely used by clinicians, its exact action, and indeed its real value, are still matters of doubt. It is believed, however, by many to have a distinct influence upon the general nutrition, and especially upon the nutrition of the nervous system. The various uses of it may be discussed under distinct headings.

First, as a Nerve Tonic.—It has been used quite largely, especially by gynæcologists, many of whom think that it has a specific direction to the genital organs, in *neurasthenia*, in *hysteria*, in *neuralgia*,—especially in *ovarian neuralgia* and in *ovarian irritation*,—and in other conditions of depressed nerve-power. It has also been much used as an alterative tonic in the treatment of the *alcohol habit*. It is true* that analysis has shown that most, if not all, of the advertised gold nostrums for the cure of alcoholism contain no gold in any form; but the most reliable obtainable information indicates that in the Keeley Institutes, so called, the treatment consists chiefly of the administration of varying doses of the gold and sodium chloride, with hypodermic injections in the interim (every three hours) of minute doses of atropine and strychnine. It is incredible that any medication can work moral reformation, and the extraordinary results which have been sometimes achieved in the Keeley Institutes are balanced by numerous failures, and have probably been only in small part, if at all, directly due to the medical treatment. Nevertheless, in some trials which we have made it did appear that the treatment just spoken of, by strengthening the nervous system and bringing about a general increase of nutritive tone, aided persons who were determined upon reform. It has seemed to us that the gold salt has some influence in overcoming the physical conditions of chronic alcoholism.

Secondly, as an Alterative.—The gold and sodium chloride has been commended by various practitioners in *scrofula*, advanced *syphilis*, *chronic rheumatism*, and *chronic diseases of the joints*. Charles G. Stockton asserts that it has a special influence upon the lithæmic and fatty degenerations which are prone to occur in advanced middle life. The salt is also employed with alleged excellent results in the various *spinal and cerebral scleroses*.

ADMINISTRATION.—The gold and sodium chloride may be given in solution or in pill, in doses of one-twelfth of a grain, increased to one-

* See *Alcoholism and its Treatment*, J. E. Usher, 1892.

sixth or even one-fourth (0.005–0.016 Gm.) three times a day. It may also be administered hypodermically, producing some pain, but usually no serious or permanent local irritation. In many cases in which it has been used the moral effect of the hypodermic injection is perhaps greater than the direct influence of the remedy.

INSOLUBLE GOLD PREPARATIONS.—The *oxide*, *iodide*, and other insoluble preparations of *gold* have been recommended as alteratives in *scrofula*, *skin diseases*, and *secondary syphilis* of various forms, in doses of from one-fifteenth to one-tenth of a grain, three times a day.

IODUM—IODINE. U.S.

Iodine is a soft, friable, opaque substance, occurring in crystalline scales with a semi-metallic lustre and of a bluish-black color. Its odor resembles that of chlorine; its taste is hot and acrid. It is somewhat volatile at ordinary temperatures, but when heated to 237.2° F. melts and emits the beautiful purple or violet vapor to which it owes its name. It is freely soluble in glycerin, alcohol, and ether, but requires five thousand times its weight of water to dissolve it. With starch it strikes a deep blue color, and this test is so delicate that it will indicate the presence of iodine in four hundred and fifty thousand times its weight of water. In testing animal liquids, such as urine, for iodine, a small quantity of nitric acid should be added to insure its being free in the liquid.

Local Action.—Iodine, when applied to any part of the body, acts as a very powerful irritant, or, if in highly concentrated form, as a mild caustic. The tincture stains the skin yellow, and causes, if applied with sufficient freedom, smarting, some erythematous inflammation, and finally desquamation. Its repeated application blisters and destroys the cuticle. Upon mucous membranes its action is more intense than upon the skin.

Absorption and Elimination.—Iodine and its salts are certainly absorbed, entering into all the tissues and fluids of the body, and, contrary to the old assertions, even into serous and other exudates (G. Leuch[1]). The iodine is eliminated partly as an alkaline iodide and partly in organic combination (E. Harnack[2]). Organic combinations of iodine used in medicine are probably broken up in the system, since Oscar Schulz[3] found that after the ingestion of the gluten-peptone-iodine preparation of C. Paal, the iodine escaped from the kidneys without the peptone. Iodine has been found in the secretions of the skin (R. W. Taylor[4]), and, according to Sée,[5] may exist in the saliva after it has disappeared from the urine. It probably escapes also to some extent from the intestines, but its chief channel is through the kidneys. In a patient under our care, taking daily three hundred and sixty grains of the potassium iodide, John Marshall recovered daily two hundred and sixty-five grains from the urine (see also Ehlers[6]). Sée states that the elimination is apt to be irregular, so that the drug may accumulate in the system.

General Action.—When taken internally, a single moderate dose of iodine causes merely some gastric uneasiness and a disagreeable metallic taste in the mouth ; when larger amounts are ingested, the gastric uneasiness may be intensified into violent vomiting, with increased salivary flow, abdominal pains, and even purging. In sufficient quantity it is a poison, although very few deaths have been recorded as caused by it. The symptoms produced by toxic doses taken into the stomach are burning pain in the œsophagus and stomach, vomiting, purging, smallness of the pulse, general deadly pallor, lessening or arrest of the urinary secretion, sometimes violent excitement with convulsions, and collapse. Twenty grains of iodine are said to have caused death, and two drachms and a half have been recovered from.* The vomit is yellowish brown or, if starchy matters have been present in the stomach, bluish. The injection of iodine into the cavities of the body for therapeutic use has several times been followed by cyanosis, thready pulse, repeated vomiting of matters containing iodine, excessive thirst, salivation, difficult urination, swelling of the eyelids, laryngeal pain, various eruptions upon the skin, high fever, and albuminuria. Sudden death may take place after some days from heart-failure.

E. Rose[7] records a death following injection of iodine into an ovarian cyst. Very soon after it was given there ensued severe thirst, with great dryness of the throat and mouth, and then painless vomiting of watery matters containing iodine. The whole surface became very pale, the extremities cyanosed, the radial pulse very frequent, but so small that it could not be counted, the urine very scanty, dark brown, and rich in iodine. After a time reaction occurred. For three days the vomiting persisted, the pulse was very frequent, full and hard, and the cheek put on the glow of high fever, but the temperature did not rise above 37.18° C. On the fourth day exanthematous blotches, not disappearing on pressure, developed on the skin and in the mouth, the sputa became bloody, and menstruation occurred two and half weeks too soon. The urine remained scanty, and on the eighth day, when all other symptoms save swelling of the parotids had disappeared, still contained iodine, and was albuminous. On the tenth day, in the midst of apparent convalescence, the patient died suddenly. In a case reported by W. O. Culpeper[8] two drachms of a tincture used externally on a child of eleven years destroyed all the skin from above the knees to below the ankles. After twenty-four hours there developed headache, backache, some diarrhœa, vomiting, great thirst, constant desire to urinate, suppression of urine, priapism, and giddiness ; finally there ensued dysentery without rise of temperature, hiccough, hemorrhage from the bowels, and great giddiness ending in death on the sixth day.

In the experiments of Jörg and his pupils, doses of iodine of a grain to a grain and a half gave rise to colicky pains, increased appetite, watery stools, an increased secretion of urine, malaise, and some headache. When the dose was augmented to two grains, a diffused sense of heat and sexual excitement were superadded. Other observers have noted this abnormal sexual excitement, and some have stated that at times it is succeeded by atrophy of the mammæ or of the testicles. Stillé affirms that

* For cases, see Woodman and Tidy, also *Münchener Med. Wochenschr.*, Feb. 1887.

the menstrual flow may become excessive, or that during pregnancy abortion may be caused. Very large quantities of iodine are asserted to have been taken without serious results. Julia de Fontenelle* tells of a man who took two and a half drachms of iodine without experiencing any remarkable effects, and Magendie relates the case of a child four years old who swallowed ten grains without serious consequences.†

In the experiments of A. Höyges and Binz,[9] preparations of iodine, potassium iodide, and iodoform in fatal doses produced in the lower animals wide-spread fatty degenerations.

If full doses of iodine be exhibited continuously for a length of time, a train of phenomena result, known as *Iodism*. In regard to these there has been a good deal of difference of opinion and statement, a difference which seems explainable only upon the supposition that different individuals are differently affected by the drug. Rilliet (Trousseau's[10] report on his memoir), who has had wide opportunities and has apparently studied the subject very closely, describes three forms of iodic intoxication: first, that in which the symptoms are those of gastric irritation; second, that characterized by nervous troubles, neuralgia, ringing in the ears, convulsive movements, disturbed intellection, with coryza, ophthalmia, salivation, vomiting, diarrhœa, polyuria, and cutaneous eruptions, and in some cases atrophy of the mammæ in the female and of the testicles in the male;‡ third, iodic cachexia, caused either by iodine or potassium iodide continuously used for many months. It is said to be most easily induced in goitrous persons, and is characterized by rapid emaciation, commencing mostly in the face, and severe nervous palpitations of the heart, with excessive appetite, which sometimes precedes and sometimes follows the loss of flesh. So long as the drug continues to be taken, these symptoms continue to progress, and after a time hysteria or hypochondriasis, with insomnia, manifests itself. The goitre, the mammæ, and the testicles waste away together; but if the medicine be suspended and health gradually returns, while the abnormal growth reappears the sexual glands remain wasted. It is probable that some of the symptoms in these cases are due to principles taken into the blood from the wasting thyroid body. The second form of iodism of Rilliet, in which the nervous symptoms are prominent, has been spoken of by other authorities; and Brodie has especially noted disturbances of vision and paralysis. In some rare cases neuralgic pains and other disturbances of nerve-functions have occurred, indicating that iodine is capable of causing a peripheral neuritis.§

The most common symptoms of iodism, as seen in the United States in non-goitrous individuals, are dull pain in the region of the frontal sinus,

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* Quoted by Stillé (*Therapeutics*, ii. 731).

† For an elaborate, careful study of the action of large toxic doses of iodine upon the lower animals, see *Hoffmann und Schwalbe's Jahresbericht*, 1879, 199.

‡ For a case of wasting of the testicles, see *Phila. Med. Times*, iv. 661.

§ See *Therapeut. Monatshefte*, 1888, iii.

coryza, sore throat, ptyalism, and an eruption upon the skin, which is usually an acne, but may take almost any shape. In its serious forms it becomes pustular or bulla-like, and may be accompanied by much dermatitis, ulceration, and even very violent constitutional disturbances. A remarkable iodic *dermatitis tuberosa* has been noted by Besnier, Duhring, and R. W. Taylor.* In rare cases there is an excessive susceptibility to iodine, often accompanied by marked irregularity of the iodic symptoms. Thus, we have seen six grains of potassium iodide given in daily dose repeatedly provoke in a man violent conjunctivitis with œdema around the eye, beginning unilaterally, but involving the whole face in a violent erythema with great subdermal exudation. Iodic accidents are especially apt to be severe when there is kidney disease, as in a case reported by F. Wolf,[11] in which forty grains of potassium iodide given in two days appear to have produced death.†

Most authorities affirm that iodine and potassium iodide produce similar symptoms. Sée, indeed, asserts that iodine exists in the blood only in the form of an alkaline iodide, while H. Kämmerer[12] and Binz believe that the iodides are decomposed in the tissues and act by the liberation of the iodine.‡ We do not think, however, that these views can be accepted as established, and the general professional belief is that the therapeutic value, and consequently the physiological action, of iodine and potassium iodide are different. Iodine is universally preferred in *scrofulosis*, the iodide in *rheumatism*. We have given the salt in enormous doses, and have seen nervous symptoms in only a single case,—a man who received for a long time two hundred and seventy grains a day, and who was intensely sleepy and stupid, presenting symptoms exactly similar to those of bromism, including an eruption of acne. Potassium iodide is said sometimes to produce sudden œdema of the glottis, accompanied by excessive dyspnœa, and ending, unless tracheotomy be performed, in death.§

The action of iodine upon the circulation has been studied by various experimenters with such alleged contradictory results that at present the most probable conclusion is that in moderate amounts iodine has little direct influence upon the circulation.

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* See *New York Med. Journ.*, November, 1888.

† See also *Journ. Cutan. and Vener. Dis.*, iv.; *Münchener Med. Wochenschr.*, xxxiii. and xxxiv.

‡ Consult also Bucheim (*Arch. f. Exper. Path. u. Pharm.*, iii.). Dubujadoux (*Gaz. Hebd.*, 1883, xx. 24) found that iodine injected into guinea-pigs suffering from malignant pustule has no influence upon the disease, even if the injections be repeated until they kill the animal, and that the blood also is as poisonous as ever to other guinea-pigs. This led him to believe that the iodine exists in the blood in a new compound which is not antiseptic. He believes this compound to be albuminous, because he has found that iodine mixed with milk or albuminous solutions soon disappears, so that it cannot be recognized by the starch test, and that shortly after this disappearance putrefaction sets in.

§ Nine cases, A. Groenouw (*Therap. Monatshefte*, 1890).

Rose[13] believed that the iodide produced a vascular spasm, but most subsequent observers have asserted that dilatation of the small vessels takes place, and Sée and Lapicque[14] believe that the potassium iodide acts like digitalis upon the heart, but that it also dilates the vessels, and in this way relieves aneurism.*

M. von Zeissl[15] asserted that the injection of the solution of iodine in sodium iodide into the jugular vein produces a temporary increase of pressure in the left auricle, with elevation of the pressure in the pulmonary arteries and pulmonic œdema, the latter phenomenon being due to narrowing of the vessels by a direct influence of the iodine upon their walls. He further affirms[16] that the injection of the iodine-iodide solution into the distal end of the carotid causes an increase of the general blood-pressure, but a much greater increase of the intra-cerebral pressure, the result of an œdematous exudation.

On the other hand, Prevost and Binet[17] have come to the conclusion, with apparent correctness, that watery iodic solutions slowly injected into the veins have no effect upon the circulation unless in overwhelming amount; nevertheless, the potassium iodide injected into the veins when in very feeble dose causes temporary rise, but when in large dose marked depression of the arterial pressure.

Action on Kidneys, and Excretion.—During its passage through the kidneys iodine undoubtedly exerts an influence upon those organs, as is shown by its producing albuminuria at times. It is indeed asserted that it occasionally causes a true tubular nephritis. The evidence as to its effect upon the solids of the urine is both contradictory and insufficient.

M. Rabuteau (quoted by Sée) dieted himself for five days, measured the quantity of urea daily eliminated, took iodine on the fifth day, and found a decided decrease in the excretion of urea. It is plain that this experimentation was too slight to be of much value, and Hermann von Boeck[18] found that the ingestion of iodine does not increase notably the elimination by the kidneys or bowels. On the other hand, M. Bouchard (quoted by Sée) declares on his personal experience that iodine does increase the daily elimination of urea, especially in diabetic patients. C. Handfield Jones[19] analyzed the urine of six patients taking large doses of potassium iodide, with the following results: first, water increased in three cases very much, in one slightly so, in two diminished; second, acidity increased in three and diminished in two; third, urea increased in three and diminished in three; fourth, phosphoric acid and sulphuric acid increased in four and diminished in two; fifth, chlorine increased very greatly in two cases, moderately in one, and decreased in two; sixth, uric acid increased very greatly in two cases and diminished in four. Eugene I. Duchesne[20] found that potassium iodide and tincture of iodine notably increased the elimination of urea, while sodium iodide was followed by a distinct decrease of this excretion. All the preparations of iodine used increased the elimination of uric acid. Henrijean and Corin[21] find that almost all of the iodides markedly increase the elimination of nitrogen as well as of the phosphates and chlorides. On the other hand, A. Haig[22] affirms that the iodides have a marked effect in lessening the elimination of uric acid and the urates, and as a result of this diminish the arterial tension.

THERAPEUTICS.—As an alterative, iodine is of especial value in *chronic scrofula*. In those cases in which there is indolent enlargement of the lymphatics, which exhibit no tendency, or but little tendency, to suppurate, it is of especial value. Except in very acute cases, however,

* See also Pierrot (*Nancy Thesis*, 1890, 310).

should always be tried, even when the glands do tend towards suppuration, especially as it exerts a very beneficial influence upon the ulcers left after suppuration. In other forms of scrofulous disease, in *chronic enlargements* of the *joints*, and *bone affections* of such nature, iodine is often of great service. As scrofulosis is generally, if not always, associated with lowered nutrition and with anæmia, cod-liver oil and iron in some form should usually be administered as adjuvants. At the same time that the drug is exhibited internally in these cases, its ointment should be freely applied to the enlarged and indurated glands. Experience has demonstrated the value of iodine in true *goitre*. All tumors of the thyroid body are not goitre, however ; cystic degeneration of it is very common, and is in no wise benefited by iodine. It is in simple hypertrophy of the gland that iodine used internally and applied externally over the tumor is beneficial. During the acute stage of enlargement the use of leeches is often of great benefit, and whenever much tenderness exists should precede the exhibition of the drug. In *phthisis* iodine sometimes does good, but only in the most chronic cases ; and inhalations of its vapors, as have been recommended by Piorry, can be of service only by stimulating the bronchial mucous membrane and the surfaces of cavities. When softening is progressing and the lung breaking down, iodine appears to hasten the process.

Local Application.—As a simple counter-irritant, iodine is very frequently employed when it is desired to maintain a mild, persistent influence, as in *chronic rheumatic affections* and sometimes in *phthisis*. For this purpose the tincture is generally preferred, and it should be applied freely once or twice a day, or every other day, according to the susceptibility of the patient's skin. In various affections of the skin iodine has been employed with asserted advantage. In *erysipelas* of the skin very beneficial results have been ascribed to its local use, but great care is necessary lest it be applied too strong. We have seen very serious results from the destruction by it of the skin in this affection. If the full strength of the tincture be used, it should be applied at first very lightly, and not more than once in the twenty-four hours. In *psoriasis*, in *acne*, and in *parasitic skin diseases* it has been used, but holds only a second rank among remedies. In a similar manner it is employed in various chronic diseases of the mucous membranes, such as *ozæna*, *leucorrhœa*, *chronic cystitis*, *chronic dysentery*, and *scrofulous ophthalmia*,—whenever, in a word, an alterative, stimulant action is desired. In cases of *retraction of the gums*, with consequent loosening of the teeth, Stillé recommends the application, with a camel's-hair brush, after each meal, of a watery solution (one grain to a fluidounce) of iodine, the mouth being immediately afterwards washed. The most important external use of iodine is as a resolvent in cases of indolent *glandular* hypertrophic enlargement, and where there are large watery exudations, as in some forms of *chronic pleurisy* and of *diseased joints*.

Iodine has been very largely employed by injection into serous cysts,

as in *hydrocele*, for the purpose of exciting inflammation and causing obliteration of their cavity; but this use of it is purely surgical, and the reader is referred to treatises upon such subjects. In chronic *empyema* the injection of iodine after free exit has been given to the pus is often of the greatest service. The solution in the beginning should be very weak, containing not more than six grains each of iodine and of potassium iodide in a pint of water; with this the pleura should be daily washed out, the strength of the solution being gradually increased.

ADMINISTRATION.—Iodine is never administered in solid form; nor should the tincture be given internally, because the iodine is precipitated by the watery juices of the stomach.

The only preparation of iodine for internal use is LIQUOR IODI COMPOSITUS—*Compound Solution of Iodine—Lugol's Solution*, U. S. (Iodine, one part; Potassium iodide, two parts; Water, seventeen parts.) As the potassium iodide holds the iodine in solution, this preparation may be freely diluted without precipitation, and may even be used hypodermically, as suggested by Da Costa,[23] in glandular enlargements. The dose is ten to fifteen drops (0.6–1 C.c.), well diluted.

For external use there are a tincture (TINCTURA IODI—seven per cent., U. S.) and an ointment (UNGUENTUM IODI: Iodine, four parts; Potassium iodide, one part; to one hundred, U. S.).

Iodine has been used hypodermically, but usually produces so much local irritation as to forbid its employment. According to A. O. Squier,[24] the following may be injected almost without causing pain.

Eucalyptol, thirty-two minims; Guaiacol, pure, sixteen minims; Iodoform, eight grains; Iodine, four grains; Oil of sweet almonds, sterilized, sufficient to make one ounce. Dose, ten to thirty minims, hypodermically.

SYRUPUS ACIDI HYDRIODICI. U. S.—*Syrup of Hydriodic Acid* is a syrupy solution, containing about one per cent. by weight of absolute hydriodic acid. For practical purposes hydriodic acid may be considered as pure iodine; so that sixty grains (teaspoonful) of the official syrup contain practically six-tenths of a grain of iodine, and are therefore equal to a little over one grain of potassium iodide. The syrup is transparent, odorless, and has a sweet, somewhat acidulous—to most persons indescribable—taste. As a simple alterative in non-syphilitic cases, from one to two fluidrachms (4–7 C.c.) may be administered, well diluted; in the treatment of syphilis it is too weak to be relied upon.

POTASSII IODIDUM—POTASSIUM IODIDE. U.S.

This salt occurs in white or colorless, generally cubic, crystals, soluble in 0.75 part of water and in eighteen parts of alcohol. If to its solution starch be added, no blue color should arise, but on the passage of chlorine the characteristic iodine reaction should take place, owing to the liberation of the metalloid by the gas; or if sulphuric acid be added, a

purple tint gradually appears, and deepens into blue : a spontaneous blue color betrays the presence of the potassium iodate, a harmful adulteration. At a dull red heat potassium iodide fuses into a crystalline mass ; by a bright heat it is decomposed.

PHYSIOLOGICAL ACTION.—Potassium iodide influences nutrition in a manner similar to iodine : indeed, most authorities teach that their action is identical ; yet in therapeutics they find a different range of employment. I. Wallace[25] has found that the iodide lessens the elimination of lime salts through the kidneys ; but his analyses were not sufficiently repeated to prove that this is a constant effect.*

THERAPEUTICS.—In certain forms of *rheumatism* potassium iodide is of value. In the early, active stages of *inflammatory rheumatism* it is useless ; but later, when the joint symptoms persist in a subacute form, the iodide comes very well into play. In *subacute* or *muscular rheumatism* the iodide is an efficient remedy. Often when the symptoms are very acute it may advantageously be combined with the alkalies, and in lingering cases, especially where there is reason to suspect a gouty taint, with colchicum. In *sciatica*, in *lumbago*, and in *rheumatic neuralgia* following exposure to cold or wet, as in all other forms of subacute rheumatism, much is to be hoped for from its use. In *gout* it is of less service than in rheumatism, but in the chronic form of the disease, and in the irregular, inherited gout which so frequently appears as neuralgia or other anomalous affection, it adds to the efficiency of small continuous doses of colchicum. In *rheumatic gout*, or *rheumatoid arthritis*, it should be tried, although little is to be hoped for from its use. There is a good deal of clinical testimony as to the value of potassium iodide given continuously between the paroxysms of *asthma*. This disorder appears at times to bear a close relation to irregular gout or rheumatism, and it is probably under these circumstances that the remedy is efficient. In *tertiary syphilis*, including in the term all cases of syphilitic bone, visceral, or nervous disease, the remedy is really of inestimable value. It must be given freely, and, when there is no cachexia, may be advantageously combined with the mercury bichloride. It is scarcely in place here to enumerate all the forms which tertiary syphilis may assume ; but the iodide is useful wherever the dyscrasia has existed for a length of time.

Potassium iodide appears to have the power of promoting absorption of serous fluids, and certainly is of value in *chronic pleuritis* with effusion, in *chronic pericarditis*, and even in *chronic hydrocephalus*.

In aortic *aneurism* large doses of potassium iodide with continuous rest in the horizontal position are much used.

In various chronic *metallic poisonings* the potassium iodide is of great service. With both lead and mercury it forms double salts, which are

* For a research upon the physiological action of large amounts of potassium iodide injected into the blood, see *Arbeiten aus dem Pharmak. Laborator. zu Moskau*, i. 125. As it does not seem to throw light upon the therapeutic use of the drug, it is not here analyzed.

soluble, and there is very good reason for believing that the formation of these salts takes place in the economy, and that the metal which has been lying in an insoluble condition in the various tissues is taken up and excreted. Severe salivation and ulcerative stomatitis have sometimes resulted from the use of the potassium salt in those who had previously taken large quantities of mercury;* and in Melsen's experiments, dogs to which insoluble preparations of mercury had previously been given without the induction of severe symptoms afterwards died under the action of the iodide, the mercury also having appeared in their urine. The experiments of Mayençon and Bergeret (quoted in the article on Mercury) afford striking confirmation of these facts, and seem to render the evidence irresistible that the iodide does cause the elimination of mercury. In regard to lead, the researches of Parkes, Goolden, Swift, Melherbe, Sieveking,† and Marshall[26] have shown that very frequently in cases of chronic lead-poisoning the exhibition of potassium iodide causes the appearance of lead in the urine. This chemical evidence is abundantly corroborated by clinical experience, so that in all cases of chronic metallic poisoning the persistent use of potassium iodide should be tried.

ADMINISTRATION.—The ordinary dose is ten grains (0.6 Gm.) three times a day, but much larger quantities may often be given with impunity, and in internal syphilitic affections may be necessary. In the latter class of diseases the best plan is to begin with twenty grains (1.3 Gm.) three times a day, and rapidly to increase the amount until drachm doses are reached, or frontal pain or other symptom of iodism produced. The best substance for disguising the very disagreeable taste of the drug is the compound syrup of sarsaparilla. UNGUENTUM POTASSII IODIDI, U. S., contains twelve per cent. of the iodide.

LIQUOR ARSENI ET HYDRARGYRI IODIDI. U. S.—*Solution of Arsenic and Mercuric Iodide* contains one per cent. each of the arsenic iodide and the red mercury iodide. It was originally suggested by a surgeon of Dublin, by whose name it is very generally known. *Donovan's Solution* is a powerful alterative, used chiefly in very obstinate chronic scaly *skin diseases*, when the local action is of a very low grade, and in *chronic rheumatism*. It is an exceedingly active preparation, very capable of acting as a corrosive poison, and when administered a little too freely is said sometimes to cause salivation. When applied locally, it acts as a violent irritant. The dose is from three to ten drops (0.2–0.6 C.c.), well diluted.

AMMONII IODIDUM—AMMONIUM IODIDE. U.S.

Ammonium iodide occurs in minute, colorless, cubical crystals, or as a white granular powder, hygroscopic, without odor when colorless, on exposure becoming yellowish, and emitting a slight odor of iodine, and

* See Budd (*Brit. and For. Medico-Chir. Rev.*, xi. 202) for a striking case.
† See Stillé's *Therapeutics*, ii. 735, Blanchard & Lea, 1864.

having a sharp saline taste. Ammonium iodide resembles closely, in its action, iodine and potassium iodide, and has been employed, both externally and internally, as a resolvent in *secondary syphilis*, *chronic rheumatism*, *incipient phthisis*, and in a variety of forms of *scrofulous disorder* with glandular enlargements. The ointment (one-half to one drachm to an ounce) has been used in *lepra*, *psoriasis*, *scrofulous glands*, etc. As the iodide is decomposed by the air, the ointment should be kept in well-stopped bottles. For internal use the dose of ammonium iodide is from three to ten grains (0.2–0.6 Gm.), in dilute solution.

STRONTII IODIDUM—STRONTIUM IODIDE. U.S.

Strontium iodide occurs in colorless, transparent, hexagonal plates, odorless, and having a bitterish, saline taste. It is deliquescent, and on exposure to air and light becomes yellow. It is soluble in 0.6 part of water at 15° C. (59° F.) and in 0.27 part of boiling water. This salt has been brought forward as a means of obtaining the alterative influence of an iodide without causing irritation of the intestinal tract or depression of the general nutrition. It contains about 56.5 per cent. of iodine, and, although its actual value has scarcely as yet been made out, may be substituted for potassium iodide in various diseases. The dose is from five to ten grains (0.3–0.6 Gm.), increased *pro re nata*. It is best administered in solution.

IODOFORMUM—IODOFORM. U.S.

This substance was discovered by Sérullas in 1822, and was introduced as a remedy by Glover in 1837, but did not become official until the 1880 revision of the U. S. Pharmacopœia. It occurs as small, pearly-yellow crystals, having a strong, persistent, saffron-like odor, insoluble in water, but readily soluble in alcohol and in ether.

Local Action.—In itself iodoform is a non-irritant, slightly desiccant powder, which appears to be imbued with local anæsthetic properties, so that the rectum may be so benumbed by a suppository containing iodoform that defecation may take place without the knowledge of the individual. By decomposition and formation of new compounds iodoform becomes a locally active substance. (See page 483.)

Absorption and Elimination.—Iodoform (or the products of its decomposition) is absorbed very slowly by the alimentary canal, but in wounds it is taken up with comparative freedom. Zeller[1] believes that there is always an albuminous compound of iodine formed at the seat of absorption. The iodine escapes from the body by all the secretions as well as by the breath, partially as an iodide, partially as an iodate, and partially in the form of a new organic compound of iodine.* According

* For an important bibliography, see the paper of M. Rummo. For details as to elimination and discussion of methods of finding the iodine in the urine, consult Johannes Grundler (*Schmidt's Jahrb.*, ccii. 232), Harnack (*Berlin. Klin. Wochenschr.*, 1883, No. 47; also *Zeits. f. Physiol. Chem.*, 1884, viii. 158), A. Zeller (*Arch. f. Klin. Chir.*, xxviii. 590), and E. Baumann (*Schmidt's Jahrb.*, ccii. 233; *Verhandl. Deutsch. Gesell. f. Chemie*, Berlin, 1882, xi. 219).

to the researches of Rummo, the elimination of iodine commences within one hour after the stomachic ingestion of the iodoform, and goes on so slowly that the haloid can be found in the urine three days later.

General Effects.—In the largest therapeutic doses (five to six grains) iodoform produces no symptoms, and we know of no cases of poisoning by its internal administration. On the other hand, its surgical use has led to a number of fatal poisonings. The symptoms, as recorded, have been very various. They may be preceded by general malaise for a day, and then suddenly burst forth.* In the most characteristic and severe class of cases the phenomena resemble somewhat those of meningitis, and may be somnolence, deepening into stupor, with contracted, motionless pupils, or restlessness, ending in active delirium, in either case the temperature being normal and the pulse exceedingly rapid. A peculiarity of these cases seems to be that death usually follows, although the symptoms have developed abruptly and the dressings have been removed at once. Schede, of Hamburg, describes six classes of cases, his sixth form being that just spoken of. 1. High fever, without other phenomena. 2. Fever, with mild gastro-intestinal irritation, depression of spirits, and rapid pulse; recovery almost invariable. 3. Very rapid, soft pulse, 150 to 180, no fever; great danger. 4. Very rapid pulse, with high fever; death almost invariable. 5. After severe operations, rapid collapse and death. A form of poisoning with melancholia, dilated pupils, and hallucinations is also described. A roseola-like dark red eruption has been noted in some cases of poisoning, and even when the constitutional symptoms are very slight there may be an extensive erythema.† In some cases of iodoform-poisoning convalescence has been very protracted, the patient remaining in a condition of unconsciousness or semi-consciousness for some days, with complete loss of memory and some evidences of mental disturbance. According to De Schweinitz, in very rare instances iodoform has produced amaurosis or amblyopia with scotomata.

On account of the indefiniteness of the symptoms of iodoform-poisoning great importance attaches to any positive means of recognizing the nature of the illness. Burlureaux affirms that if a piece of silver be placed in the mouth of a person suffering from iodoform-intoxication, the taste of garlic will be immediately perceived, and that if some of the saliva be mixed with calomel, a canary-yellow precipitate of mercurial iodide will be obtained; according to Sasse, if a pinch of powdered calomel be placed upon a saucer, and a few drops of the urine from a case of iodoform-poisoning be mixed with it by means of a glass rod, the yellow color will appear (yellow iodide). These tests prove only that the patient is under the influence of some compound of iodine, but, if correct, must in many cases be sufficient for the purposes of the practitioner.

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* Case, *Deutsch. Med. Wochenschr.*, ix. 443.

† Cases, *Intern. Cong. Copenhagen*, 1884, Sect. Dermatol., 118.

Notwithstanding numerous experiments upon the lower animals, further research is necessary before any positive knowledge can be reached as to the physiological action of iodoform, although it is probable that it acts very much as does iodine.

The symptoms produced by iodoform in the frog are said to be muscular relaxation with sometimes, at a later stage, convulsive movements. In the higher animals large but non-toxic doses produce symptoms of intoxication, tottering, weakness, and loss of appetite, but no vomiting ; fatal doses cause anæsthesia, narcosis, convulsions, with violent opisthotonos, hurried or irregular breathing, slow, feeble pulse, and finally death. A. Höyges[2] found that in dogs and cats toxic doses caused deep sleep without loss of reflex activity, but that in rabbits no sleep resulted. Very frequently after these large doses, especially when they are repeated, there is great gastro-intestinal disturbance, as is shown by vomiting, diarrhœa, and dysentery, with bloody discharges. The action of the drug upon the circulation has been especially studied by Rummo.[3] He finds that in the frog the rate of the cardiac pulsations is lessened, and for a time the energy of the ventricular systole is increased, but afterwards the pulsations become feeble, and finally the heart is arrested in diastole ; the contractions cannot be re-established by the use of atropine. In the mammal the rate of the pulse is decreased, and after small doses the arterial pressure is at first increased. By large doses the pressure is much diminished. Section of the pneumogastrics does not affect the cardiac action of the drug. After very large doses there are albuminuria and even hæmaturia.

These various researches would indicate that the iodic compounds liberated by iodoform are universal poisons, and that the conclusion of Rummo is corrrect,—namely, that iodoform acts upon almost all the tissues, but primarily upon the nerve-centres and subsequently upon the nerve-trunks and on the muscles.

After death from iodoform a very wide-spread fatty degeneration is to be found. This change appears to commence in the liver and rapidly to involve all tissues of the body. Floucaud[4] states that there is a very distinct alteration of the blood-corpuscles.

THERAPEUTICS.—At one time iodoform was used to a considerable extent as an internal alterative and analgesic in *chronic syphilis*, especially when there were severe *rheumatic*, *neuralgic*, or *night-pains*. It has also been employed as an absorbefacient substitute for iodine in various *lymphatic tumors* and *serous effusions*. In syphilis various clinicians have borne testimony to the advantageousness of its hypodermic use, three to five grains a day. It seems to have, however, no superiority over the simpler iodine preparations, and to be much less certain and definite in its action, so that its internal use has passed completely out of vogue. On the other hand, as a local remedy, it has continuously asserted itself in the face of very numerous substitutes, and is used to-day as frequently as it ever was. It is useful in cases of painful *ulcers*, even when they are *cancerous*, serving to alleviate pain and to promote cicatrization. At first employed especially in *syphilitic affections*, it is now known to act

equally well in *indolent leg ulcers*, in *burns*,* and in other non-specific abrasions, and it is thought to be not only a local anæsthetic, but also a decided stimulant to nutrition. Within the last few years it has been very freely employed as an antiseptic dressing to *wounds*, and the testimony is so strong that it is difficult to avoid believing that it is one of the most reliable of the antiseptics. It is, however, affirmed to have no power in preventing erysipelas, and used freely is very dangerous to the patients. It is employed either in the form of powder dusted in the wound, or as dressings saturated with it, the first method being at once the more effective and the more dangerous.

The danger of iodoform-poisoning in a surgical case varies not only with the amount of iodoform used, but also with the form of the iodoform and the seat of the application. The more finely powdered the iodoform the greater its activity, and serious absorption is especially apt to take place from the peritoneal surfaces.†

In 1886 Fürst described furuncular and eczematous inflammation produced by the contact of iodoform with the skin. Krevet[5] affirms that this irritation can rapidly be relieved by momentary applications of very hot water to the part.

The good results which have followed the surgical use of iodoform as an antiseptic dressing have led to a series of investigations as to its action on the lower organisms, with results which are apparently at variance with previous surgical teachings. In November, 1886, De Ruyter announced at a meeting of the Berlin Surgical Society that the powder of iodoform has little or no effect in preventing the development of bacteria, and that when it is mixed with rapidly infective bacteria, like those of anthrax, it does not sensibly influence the development of the disease which is caused by inoculation with the mixture. This has been confirmed experimentally by Kronacher,[6] who employed the bacteria of erysipelas and of anthrax; also by P. Baumgarten,‡ who further found that iodoform powder mixed with the tubercular bacillus in cultivating apparatus did not prevent its ordinary development, and that the bacillus mixed with iodoform powder when introduced into guinea-pigs and rabbits produced rapid tuberculosis; also by Lübbert,[7] with the Staphylococcus pyogenes; also by Chr. Heyn and Thorkil Drovsing,[8] who found that iodoform has no influence upon the development of the Staphylococcus

* *Burns, Treatment of.*—At a discussion of the International Congress of Dermatology, in 1889, the conclusion was reached that the best treatment of burns in the beginning is to cut the bullæ, wash the part with a very weak solution of salt, and then dress with iodoform gauze, or a pomade of iodoform, and cover with oil-silk. In the later stages, after the separation of the eschars, according to Hebra, iodoform retards cicatrization, whilst a one or two per cent. solution of resorcin hastens epithelium formation.

† In a case in which an extensive intra-peritoneal dressing of iodoform gauze was used, and seven grains of calomel given by the mouth, violent irritant poisoning, with numerous bloody mucous stools at short intervals, occurred, evidently as the result of the formation of the mercurous iodide in the alimentary canal.—F. F. Simpson in a letter.

‡ A curious fact made out by Baumgarten was that rubbing the bacillus of anthrax with any hard powder apparently mechanically kills the organism.

pyogenes or of the coccus of pneumonia or of the Bacillus subtilis and other organisms, and conclude that it is not only worthless as an antiseptic, but may even be the means of carrying the septic organisms into the system; also by Johann Olsen,[9] with various bacterial organisms; also by Könige.[10] On the other hand, H. Sattler,[11] in his experiments, found that when he impregnated threads with iodoform and micro-organisms and then placed them in culture-apparatus, the iodoform had a very distinct effect in checking the development of the bacteria, and De Ruyter states that if instead of using the iodoform powder he employed an ethereal solution in which decomposition of the iodoform had already commenced, there was a distinct effect upon the organisms. In a further series of experiments De Ruyter showed that iodoform is decomposed by blood, serum, and other organic fluids in which micro-organisms are growing, and apparently proved that the decomposition is produced by the ptomaines developed by the growing organisms. These general results have been abundantly confirmed ;* the antiseptic properties of iodoform depend upon its decomposition, and its action is most favorable when the processes of fermentation and of chemical activity are most energetic.†

The clinical results achieved by surgeons are so concordant and so decided that the practical value of iodoform in the treatment of wounds and ulcers must be considered established. It is possible that a part of the good influence of the iodoform is due to a specific effect upon the tissues of the wounds. Further, the powder of iodoform may have a very distinct protecting power both mechanically and by the dryness of the wound which it maintains, the discharges from the wound being the especial soil in which the bacteria develop. In tubercular diseases iodoform appears to exert a direct influence upon the bacilli. Many clinicians bear strong testimony to the effect of iodoform on *tubercular ulcers* of the larynx and other organs. According to Bruns,[12] the first change which results from the use of iodoform in a tubercular abscess is the disappearance of the bacilli and the appearance of normal granular tissues. The value of iodoform as a local application in surgical tuberculosis seems to be firmly established. In the treatment of *tuberculous abscesses*, in *tuberculous empyema*, in *tuberculous joints*, in non-suppurating *tuberculous glands*, and even in *tuberculous peritonitis* numerous cures have been reported. That the iodoform has a specific influence upon the tubercular organism would seem to follow from the experiments of Gosselin, of Caen, who found that guinea-pigs saturated with iodoform are incapable of contracting tuberculosis. The manner of application varies with different surgeons. Verneuil, who has had an enormous experience, prefers, in the treatment of abscesses, tuberculous glands, and in most other

* See especially Neisser (*Virchow's Archiv*, cx.), Schnirer (*Wien. Med. Presse*, 1887, cx.), and Kuntz (*Beiträge Path. Anat. u. Physiolog.*, 1888, ii.).

† Moeller has found that the *iodates* and *iodic acid* cause symptoms similar to those produced by iodine (*Inaug. Diss.*, Bonn, 1877), and Schwerin has shown that *methyl iodide* is also anæsthetic and hypnotic (*Centralbl. f. Med. Wissensch.*, 1884, 146).

cases, the injection of a five per cent. ethereal solution. Others prefer glycerin as a menstruum, especially in empyema ; whilst others, particularly in peritonitis, dust the dry powder over the portion which has been laid open.

ADMINISTRATION.—Iodoform may be applied to ulcers in powder, in solution, or in ointment (UNGUENTUM IODOFORMI—ten per cent., U. S.). When there is a great deal of pain, especially if there be much discharge, the powder may be preferred ; not more than half a drachm of iodoform should ordinarily be applied to a wound, although in cases of tuberculosis the surgeon is more than warranted in taking the risk of larger amounts. Verneuil injects at one sitting never more than seventy-five grains of the iodoform. In *uterine cancer* and in painful *hemorrhoids* cacao-butter suppositories, containing from five to ten grains of the drug, may be employed. Owing to the bad odor of the drug, its application about the mouth and throat is often objected to.

According to Lewis Elsberg,[13] if to four parts of absolute ether one part of crystallized iodoform be added, and the whole shaken in a *red* glass flask, a solution is obtained of sufficient strength for effectual use in diseases of the mouth, and free from odor other than that of ether. Olive oil, saturated with camphor, is said to dissolve six per cent. of iodoform, and is preferred by some surgeons.

The quantity required to take life is uncertain. Langenstein[14] attributes a death to four grammes. The cause of death seems, however, doubtful. Czerny[15] reports death from six grammes, not doubtful.

TOXICOLOGY.—Whenever any suspicious symptoms arise during the use of iodoform, the dressing should immediately be removed and the part well washed with warm water. The assertion by Samter and Retzlaff,[16] that the potassium bromide is a chemical antidote by virtue of its dissolving iodine compounds, has, so far as we know, received no clinical or experimental confirmation, and there appears to be no other treatment of iodoform-poisoning than the free internal use of water, with the hope of aiding in the elimination of iodine compounds, and the meeting of symptoms as they arise.

IODOL.

Iodol, which is made by the action of iodine upon pyrrol, is a yellowish-brown, shining powder, composed of long, prismatic crystals soluble in three parts of absolute alcohol, in ether, and in fatty oils, but soluble in water only in the proportion of 1 to 5000. It is tasteless and without odor. It contains 88.9 parts per hundred of iodine, as contrasted with 96.7 parts contained in iodoform. First discovered by Silber and Ciammican, it was proposed as an antiseptic by G. Mazzoni,[1] of Rome. It causes in the lower animals (Marcus[2] and T. Pahl[3]) emaciation, albuminous urine, fall of temperature, general loss of muscular power, and finally death from fatty degeneration of the liver, kidneys, and other tissues. The assertion that it is not capable of producing constitutional

symptoms is not correct. C. Lanenstein [4] reports, as caused by the surgical use of the drug, dizziness, marked rise in the temperature, vomiting, small irregular pulse of 136, albuminous urine, and apathy, which did not subside for four days. Iodine was found in the urine for two weeks.

In the experiments of Seifert, iodine was first detected in the urine and saliva twelve hours after the ingestion of seven and a half grains, did not reach its maximum until eighteen hours, and continued present for three full days: this accords with the statement of Pick [5] that iodol is absorbed very slowly. This slow absorption is probably the reason that it is a less dangerous topical application than is iodoform.

Cervesato [6] affirms, with doubtful correctness, that in man iodol, taken internally, acts like preparations of iodine, but never causes iodism.

THERAPEUTIC USE.—Iodol may be employed for all purposes for which iodoform has been used. Mazzoni's solution was—iodol one part, alcohol sixteen parts, glycerin thirty-four parts. One drachm of iodol forms with one ounce of ether a clear brown solution, which may be applied by the spray or brush to the nasal and other mucous membranes, upon which it leaves a coating of iodol. Iodol has also been used as an internal remedy. According to Assaky, iodol is very effective in *tertiary syphilis* in doses of from six to thirty grains (0.4–2 Gm.) a day.

ARISTOL or *Annidaline* is a light, reddish-brown, odorless, crystalline powder, insoluble in water, very soluble in fats and ether, slightly soluble in alcohol. It is a substitution compound, having the chemical name *dithymol-diiodide*, and containing 45.8 per cent. of iodine. According to Neisser,[1] Quinquaud and Fournioux,[2] and Eichhoff, when introduced even in very large amounts into mammals it produces no serious intoxication. The method of its elimination has not been made out. Quinquaud and Fournioux recognized the presence of iodine in the urine of animals to which it had been freely given, but were not able to discover traces of thymol. The experiments of Neisser seem to show that it has no influence upon the lower organisms, and it cannot be considered, therefore, as directly antiseptic. It has been employed by a number of practitioners with asserted good results as a local application in inflammations of the mucous membranes of the nose and upper air-passages, especially when there is absence of secretion; also in *psoriasis*, in *lupus*, in various *syphilitic lesions*, and as a substitute for iodoform in the treatment of *wounds*. It appears to be free from irritant properties, and may be used in a strength varying from ten per cent. to the pure powder.

Through the ingenuity of pharmaceutical chemists there have been put upon the market a number of iodine compounds, very few of which have real value.

NOSOPHEN, the acid *tetra-iodo-phenol-phthalein*, is an impalpable, yellow-gray, odorless, tasteless, insoluble powder, containing sixty-one

and seven-tenths per cent. of iodine. Its sodium salt, *Antinosine*, is a dark blue amorphous powder, readily soluble in water and alcohol. Its bismuth salt, *Eudoxine*, is a reddish-yellow, tasteless, odorless, insoluble powder. It is alleged that nosophen and antinosine are not decomposed in the human body, whilst eudoxine is slowly changed by the alkaline juices of the intestines into antinosine and bismuth. It is alleged also that they are germicides. As intestinal antiseptics, eudoxine being the best, they may be given in doses of five to eight grains (0.3–0.5 Gm.).

Locally, antinosine, on account of its solubility, is preferred as an application in infective inflammations of the mucous membrane, the strength of its solution varying from one to three per cent. According to Binz and Zantz, when given intravenously, antinosine is decomposed and nosophen precipitated in the blood.

EUROPHEN, *di-isobutyl-ortho-cresol-iodide*, is a yellowish amorphous powder, containing twenty-eight and one-tenth per cent. of iodine, which is stated to be decomposed more slowly than iodoform, and to be therefore less poisonous. Taken internally, it escapes unchanged in great part or altogether with the fæces, and is said to be non-toxic, fifteen grains producing no effect in human beings. Externally, it is employed to a considerable extent as a substitute for iodoform, but appears to have some irritant properties.

SOZIODOL, *diiodparaphenolsulphonic acid*, contains thirty-one and a half per cent. of mercury and thirty-eight per cent. of iodine ; it is used as a local irritant, chiefly employed in the form of a powder (talc), fifteen per cent. The assertion of A. Lübbert, that it is as active as corrosive sublimate as a germicide, and free from poisonous properties, has not been confirmed.

IODOFORMOGEN, a compound of albumin and iodoform, nearly free from odor, is a light yellow powder, insoluble in water, which has been used as a substitute for iodoform.

OLEUM MORRHUÆ—COD-LIVER OIL. U.S.

Cod-liver oil is obtained from the liver of Gadus morrhua and other species of Gadus. In the manufacture of the so-called *Shore oil*, the only variety employed in medicine, the fish caught near land are brought at once to the shore, and the oil is obtained by forcing steam at high pressure through a mass of the fresh livers enclosed in a metallic vessel, so as to tear them into pieces and melt out the oil. Cod-liver oil for medicinal purposes should always be perfectly limpid, yellow, free from rancidity, and have the peculiar taste and smell of the oil well developed. The cruder varieties, sometimes known as *Straits* or *Banks oil*, used in the preparation of leather and for other purposes in the arts, are prepared by allowing the livers to stand in casks and undergo putrefaction until

the oil rises to the top, when it is skimmed off. The black or brown oil which results is extremely disgusting both in odor and taste, and is loaded with the products of decomposition.

Cod-liver oil is a very complex substance, containing glycerin, oleic, margaric, butyric, and acetic acids, gaduin, various biliary principles, iodine, chlorine, traces of bromine, phosphorus, phosphoric acid, and a peculiar ammoniacal base, *trimethylamine* (commercial *propylamine*), which exists in no other official oil, but occurs in ergot. According to the U. S. Dispensatory, the proportion of iodine never exceeds 1 part in 2000. *Gaduin* is a peculiar, dark brown substance, which is probably medicinally inert.

PHYSIOLOGICAL ACTION.—As is well known, all fatty substances when taken into the system have a tendency to cause deposition or formation of fat in the body. Cod-liver oil certainly shares this property in an eminent degree. Pollock (quoted by Stillé) has found that if there be given of it to pigs from one to two ounces *per diem*, to sheep one ounce, and to bullocks from three to nine ounces, it is digested, and aids in fattening the animal ; larger amounts than those noted in Pollock's experiments always derange very seriously the digestive function. No close studies of the effect of cod-liver oil upon healthy men have been made. Undoubtedly it tends to produce obesity ; but, as no other oil is able to supply its place in various chronic diseases, it must have some influence upon nutrition not shared by ordinary fatty matters, and therefore is an *alterative*.

The history of the clinical use of oleum morrhuæ certainly indicates that it influences the constitution of the blood. It is an every-day occurrence to see pale, anæmic patients become, while taking it, rosy and plethoric. According to the analysis of the blood of a patient made by Simon, there is, during its use in *phthisis*, a great increase in the amount of solids in the blood, a diminution of the fibrin, and an increase in the albumin. The examinations of Dugald Campbell[1] have confirmed the results of Simon. It is very probable that cod-liver oil has some peculiar influence upon the blood-making organs. Upon the various single functions of the body, except the digestive, cod-liver oil has no apparent immediate effect, disturbing directly neither the nervous, motor, respiratory, circulatory, nor secretory movements. When by its use the general nutrition is improved, all the functions seem to share equally in the improvement. Cod-liver oil has undoubtedly, when given with sufficient freedom, a tendency to cause indigestion and looseness of the bowels. All oils are of difficult digestion, and when too much of the oleum morrhuæ is exhibited in man, as in animals, it exerts a deleterious local effect upon the alimentary apparatus.

Much speculation has been indulged in as to which of the ingredients of cod-liver oil impart to it its peculiar medicinal properties.* Certainly,

* A Gautier and J. Bouillot assert that they have found in cod-liver oil certain alkaloids which are stimulants to the circulation and to the nutrition, and also to the kidneys,

however, no conclusion has been established, and the present probabilities are that it acts as a whole,—*i.e.*, that its virtues depend upon the peculiar combination.

The experiments of Oswald Naumann[2] indicate that the physical properties of cod-liver oil aid in its usefulness. He first tested the rate at which various oils pass through fresh moist animal membranes when pressed upon by a column of mercury or by the weight of the atmosphere over an exhausted receiver, and found that cod-liver oil passed much more rapidly than did any of a number of oils tried. Apparently this power depended in some measure upon the presence of the biliary principles, since if it was deprived of them the rate of its passage was greatly lessened, but was again increased by the addition of a little bile. The investigator then, opening the abdomen of cats, separated in each animal by ligatures two knuckles, of equal length and entirely similar, from the remainder of the intestines. Into each of them he injected a certain amount of bile, and then into one ordinary oil, into the other cod-liver oil; and when the animals died, some hours afterwards, it was always found that much more of the cod-liver oil was absorbed than of the other oil. Naumann's experiments were too few and incomplete to be decisive, but they accord with the clinical observation of Berthé,[3] who found that cod-liver oil could be taken longer than other fats without appearing in the fæces; observations which have been confirmed by Bucheim,[4] as well as by J. Gad.[5] Both Bucheim and Gad believe that this absorbability depends largely upon the presence of free fatty acids in the oil, but it is probably due to the biliary matters, since H. A. Hare[6] finds it greatly increased by the addition of taurocholate and glycocholate of sodium. Hare asserts that cod-liver oil impregnated with a small quantity of the biliary salts is rapidly absorbed when rubbed upon the skin, and proposes the practical use of the mixture.

Naumann's last series of experiments were directed to discovering the comparative ease with which animal oils and the cod-liver oil were oxidized. For this purpose he used a test-solution of potassium permanganate, and on adding to given bulks of this, in test-tubes, equal amounts of the various oils, noted the changes of color induced by the reduction of the permanganate. He found that cod-liver oil was the first to be affected.

It is evident that the power of being easily absorbed and easily oxidized fits a fat for use in the animal economy; but even if cod-liver oil possesses these properties to a remarkable degree, it is clear that they cannot be the chief causes of its peculiar influence on disease.

THERAPEUTICS.—Cod-liver oil is especially useful in that condition of the system in which, with generally lowered tone, there is a tendency to hyperplasia and to the formation of exudations composed of abnormal cells, which in the great majority of cases from the very beginning are incapable of developing into perfect tissue, having but one potential quality, that of dying. There are several types of this condition of the system. In one of them there is a tendency to tissue-increase in the lymphatic glands, which is expressed in the multiplication of their cellular elements, somewhat modified in their morphology, through the operation

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and to which are largely or altogether due the peculiar properties of the oil. These alkaloids have been used in practical medicine by J. Bouillot, who affirms that 0.15 to 0.25 gramme given during the twenty-four hours powerfully stimulates nutrition, increasing very much the amount of the urine and also the nitrogenous elimination, especially of the completely oxidized nitrogen (*Compt.-Rend. Acad. Sci.*, 1892, cxv.).

of a definite morbific cause,—the bacillus tuberculosis,—and finally to their necrosis. The death of these cells is due partly to those inherent qualities, which prevent them, because of their abnormal status, from remaining as they are or from developing further into perfect tissues; but chiefly because of the presence of a poison derived from the peculiar micro-organism which in the first place called them into being and now causes their destruction. These cells undergo hyaline and fatty degenerations and metamorphoses. When the process is slow, little fluid is exuded from the blood-vessels and cheesy deposits are formed; when more rapid, with abundance of moisture, a creamy fluid resembling pus is produced. This latter material is, however, not true pus, but consists only in small part of preserved, emigrated leucocytes, while it is chiefly made up of degenerated cells and fatty detritus admixed with lymph. In either case, owing to the tendency of the pathological condition, originating in the glands, to invade the surrounding parts, ulceration is the final result. This condition is the so-called *scrofulous diathesis*,—*scrofulosis*.

In another group of cases the parts and organs attacked are the mucous membranes, the lungs, the kidneys, the liver, etc. In these situations the entrance of the bacillus tuberculosis sets up a cellular multiplication and exudation, with the production of new formations which present a typical histological structure, to which we give the name of tubercles. Similar structures also exist in the lymphatic glands prior to the secondary changes which result in the breaking down and ulceration of these parts. The lungs, on account of their relations to external nature, are especially exposed to the entrance of infected material in the form of dust or spray, which tends to set up, especially in their apices, pathological states of the nature just described, or to produce a freer and more rapid multiplication of the lining cells of the alveoli, and a freer exudation from the blood-vessels, resulting in consolidation. The solidified lung tends ultimately to become cheesy, to break down, and to ulcerate. In this way "consumption," with ulcerative and bronchiectatic cavities, comes to be formed. Attacks of pneumonia, the ultimate result of some exposure, through the accidental introduction of material charged with the bacillus tuberculosis, may, because of the previous pathological condition, afford more favorable opportunities for the development of this germ, which, bringing about cheesy metamorphoses of the exudate, produces a more rapid phthisis.

There are various diseases of the bones, depending upon or resulting from tubercular deposits—so-called scrofulous taint—elsewhere in the body, which are most favorably affected by cod-liver oil. Sometimes the disease attacks the articulated surfaces, giving rise to chronic tuberculous inflammations of the joints,—*white swellings*; sometimes it is the body of the bones, especially of such as are composed chiefly of spongy tissue, that is affected, producing *tuberculous osteomyelitis*,—*caries*, *abscesses*. In this, as in all other forms of tuberculosis, cod-liver oil is almost a specific.

Another affection, which depends upon certain nutritive disturbances in the body, is *rickets;* cod-liver oil is of great value in this complaint. In certain pale, cachectic children there may be found a swollen, tumid belly, perhaps with evident enlargement of the liver and sometimes of the mesenteric glands. This is the so-called *tabes mesenterica*, a condition depending upon the development of tubercular processes in the mesenteric glands, which is sometimes relieved by the exhibition of cod-liver oil.

The value of cod-liver oil in what is often very incorrectly called the *pre-tubercular* stage of phthisis has already been mentioned, but is so important that it will bear reiteration. There can be no doubt that consumption may commence with catarrh. Whenever a patient is feeble, pale, somewhat anæmic, and complains of his liability to catch cold on the slightest exposure, even though no demonstrable local disease exists anywhere, or rather because no such local disease exists anywhere, there is cause for alarm ; and it is of the most vital importance that the patient be put upon a tonic treatment whose basis is cod-liver oil, be fed upon nutritious diet, and have the hygiene of his daily life regulated, especial care being taken to avoid any exposure to cold. In the advanced stage of chronic *phthisis* the remedy is less efficacious ; yet it does more good than all the other remedies of the Pharmacopœia combined,—alleviating the cough, increasing the strength, weight, and general health of the sufferer, often retarding or even arresting the pulmonic disorganization, almost always greatly prolonging life, and in rare instances, in conjunction with other measures, effecting a cure. It is a question of some importance to decide how the remedy does good in these cases. Its influence during phthisis is not directly upon the local lesion, but upon the general condition of the system. The general symptoms usually commence to improve before the local lesions, and sometimes, although the patient fattens and gets stronger for a time, the pulmonic affection steadily increases ; again, in some instances the oil fails to increase the weight of the patient or sensibly to affect the general nutrition, and in these cases it never does any good. In acute, disseminated *tuberculosis*, cod-liver oil, like all other remedies, is of very little, if any, value.

In cases of *defective nutrition*, when pallor, anæmia, loss of strength, and, perhaps, emaciation occur without any obvious cause, cod-liver oil is often of great service, especially when the subject is a child.

In persons broken down with any of those chronic diseases which take the form of dyscrasia the remedy is often of great service. Thus, in the cachexia of *tertiary syphilis* it is invaluable. The disease by whose relief and cure cod-liver oil first achieved its reputation is *chronic rheumatism*. We think, however, that it is much more efficacious in those cases in which the rheumatic disease has been grafted upon a scrofulously tainted constitution, or in those in which the patient has been broken down by the disease, or by other agencies, so that there is what may be styled a general nutritive dyscrasia, than in simple chronic rheumatism ; yet in obstinate *sciatica* and *lumbago* trial of it should always be made. In *gout*

oleum morrhuæ is of little service, and should be used only in the very chronic form of the disease, and when there is a generally disordered nutrition.

In *nervous affections*, especially in *neuralgia*, in *skin diseases*, in fact, in any chronic disorder in which the patient is feeble and presents a condition of general depraved nutrition somewhat similar to that seen in consumption, cod-liver oil may be exhibited with advantage.

ADMINISTRATION.—The chief difficulty in the use of cod-liver oil is the very common, real or imagined, inability of the patient to take it. Without doubt, this very often arises from its nauseous taste, to lessen or disguise which various expedients are resorted to.

Sometimes a piece of salt taken into the mouth just before the oil, which is also immediately followed by another lump of salt, suffices. It is said that some prefer the oil in emulsion made with some strong aromatic water. The addition of an equal part of glycerin and one-half to one drop of the oil of bitter almonds to the dose certainly lessens the taste of the medicine. Some patients take the oil best in the froth of ale or porter, the glass being first half filled with the malt liquor, then the oil carefully floated on the top without touching the sides of the glass, and the remainder of the vehicle put upon the top of it. Most of the patients requiring oil are also benefited by the use of alcohol; and our experience with the remedy is that the most generally successful plan of exhibition is to place, according to the exigencies of the case, from one to three tablespoonfuls of whiskey or brandy in a tumbler, add a small amount of water, put the oil in the centre, and *toss* the whole down the throat, the head being held well back, the mouth wide open, and the lips not touched by the medicine. The stimulus of the alcohol often enables the stomach to digest the oil when otherwise it could not do so. Sometimes it is necessary to commence with a single small daily dose, even a single teaspoonful, which is best taken at bedtime, and gradually to increase the amount as the patient becomes habituated to it. Children almost always learn to tolerate the taste of the oil, or even become in a short time fond of it.

The usual dose of cod-liver oil is for an adult a tablespoonful three or four times a day; for a child one year old, a teaspoonful. When infants cannot digest cod-liver oil, inunctions may sometimes be practised with advantage. N. A. Randolph and A. E. Roussel[1] state that they have seen in such cases the oil appear in the fæces.

ACIDUM PHOSPHORICUM—PHOSPHORIC ACID. U.S.

Phosphoric acid, which results from the burning of phosphorus in the air, is prepared by the action of sulphuric acid upon bone-ash, which consists chiefly of calcium phosphate. The official acid is the tribasic acid of chemists.* ACIDUM PHOSPHORICUM DILUTUM, U. S., contains ten per cent. by weight of absolute orthophosphoric acid. It is a colorless, inodorous, sour liquid, of a syrupy consistence, which has a very acid reaction, but is not corrosive to animal tissues.

THERAPEUTICS.—Phosphoric acid has been used considerably as a

* It has been affirmed that the *bibasic pyrophosphoric acid* is a cardiac sedative (see *Journ. of Anat. and Physiol.*, xi.).

tonic and alterative, especially in scrofulous diseases, but seems to have no other value than that of a very feeble and doubtful stimulant to the digestive apparatus. It may be given in doses of five to fifteen drops (0.3–1 C.c.), well diluted.

GLYCERO-PHOSPHORIC ACID.—As is well known, the nervous tissues of the body contain a notable percentage of phosphorus. It is present in the form of glycero-phosphoric acid. This fact has led to its employment as a nerve tonic in such conditions as *neurasthenia*, *locomotor ataxia*, and *phosphaturia*, with results asserted to exceed those obtained from phosphorus in any other form. It is given either in the form of the acid itself or of sodium or calcium glycero-phosphate in doses of two to five grains (0.1–0.3 Gm.).

CALCIUM PHOSPHATE.—Calcium phosphate is an abundant ingredient of bone, but also exists in notable quantities in all the tissues, and is probably as essential to their health as to that of bone. Whenever it is taken out of the food of animals, although they be otherwise well fed, sooner or later they waste, sicken, and die.

Chossat[1] fed pigeons exclusively on corn containing very little of the calcium phosphate, and found that after some months they wasted, were affected with diarrhœa, and died. According to Roloff,[2] a herd of cows which had been fed upon hay from a certain meadow were very much out of health, and suffered from *fragilitas ossium*. On examination, the hay was found to be nearly free from earthy salts, and upon bone-meal being given to the cows they recovered their health in four weeks. The same authority further states that in some meadows with which he is acquainted the disease is endemic among the cows because the grass is so poor in phosphates. Haubner[3] also affirms that cattle fed exclusively upon potatoes, or upon roots very poor in phosphates, fail to fatten, become weak, and are apt to suffer from caries, but that if the calcium phosphate be given they rapidly improve; and E. Voit[4] states that rachitis without emaciation can be produced in three or four weeks in young dogs by taking the calcium phosphate out of the food.

Hegar[5] has considered the absorption of the calcium phosphate, when given as a medicine, very doubtful, because when he exhibited it freely there was no increase in the amount of the phosphoric acid or of the earthy bases in the urine. Böker,[6] on the other hand, has found that if the drug be given to those wet-nurses whose milk contains an abnormally small amount of phosphates, the milk soon becomes rich in the earthy salts, and L. Perl[7] has found that administration of the phosphates is followed by an increase in their amount in the urine. Further, Albert Riesell[8] has shown that the phosphates are eliminated by the intestines, and therefore that even if it were a fact that their renal excretion is not augmented by their administration, it would not prove that they are not absorbed. Teissier[9] has found that in the early stages of phthisis there is a very great increase in the excretion of the earthy phosphates by

the kidney, and the researches of Beneke* are said to have shown that this increased renal elimination, which plainly occurs in several allied diseases, is not accompanied by any increase in the amount ingested in the food or decrease of the amount eliminated by the intestines, and that, consequently, there is a very decided wasting of the normal phosphates of the body. This being so, the use of phosphates in these diseases is as rational as that of iron in anæmia.

THERAPEUTICS.—According to Dusart,[10] to Beneke, and to Teissier, the diseases in which the calcium phosphate is especially indicated are *rachitis*, *osteomalacia*, *phthisis*, and *scrofulosis*. It is evident that the indications for the earthy salts are very strong in the first two of these affections, and clinical experience has certainly borne out the results of *a priori* reasoning. In *scrofulosis* the call for the drug is not so plain; but Beneke states that in many cases, if the urine be examined, it will be found to be abnormally rich in earthy phosphates, and that under these circumstances the remedy is of the greatest value. Cases are not rare of children of slow development, often seemingly well nourished and robust, and yet really pale and with flabby flesh, but without any distinct symptoms or marks of scrofulosis or of rachitis. Under these circumstances, the child is in a condition allied to that of the diathesis spoken of, and calcium phosphate is serviceable. In cases of *delayed union* after *fracture* the present remedy is seemingly indicated, especially since Dusart has experimentally proved that when given to animals whose bones have been broken it hastens union and makes the callus abnormally heavy and firm. Calcium phosphate has been recommended in various diseases other than those mentioned, but its value in them is much more doubtful. Bennett commends it in *chronic phthisis*; Piorry,[11] in *syphilitic periostitis*; Beneke, in *syphilitic gummata*; Schönian, and also Kugelmann, in the *menorrhagia* of anæmic women. Beneke calls attention to the use of it during *pregnancy*, and believes that it exerts an influence on the fœtus, so that women who have borne only rachitic children will bring forth healthy offspring.

ADMINISTRATION.—The U. S. Pharmacopœia recognizes the *Precipitated Calcium Phosphate* (CALCII PHOSPHAS PRÆCIPITATUS), a white, inodorous, tasteless powder, which is prepared by dissolving bone-ash in muriatic acid and precipitating with ammonia. This may be employed in doses of ten grains (0.6 Gm.) three or four times a day, but, owing to its insolubility, is not so useful as the so-called *lactophosphate of lime*. This preparation, originally suggested by Dusart and Blache, is made by the action of lactic acid upon calcium phosphate, and was found by those experimenters to be soluble in all proportions not only in water but also in the gastric juice. Almost invariably with children, when calcium phosphate is indicated, it is best given in the form of the *emulsion of cod-liver oil and lactophosphate of lime*, which as usually prepared contains

* We have not had access to the original memoir of Beneke (*Zur Würdigung des Phosphors Kalkes in physiolog. und therapeut. Beziehung*, Marburg, 1870). See *Schmidt's Jahrb.*, cli. 138.

fifty per cent. of cod-liver oil and two grains of the lactophosphate to the drachm. This emulsion, which usually agrees better with the stomach than other preparations of cod-liver oil, may be given in doses of from one teaspoonful to a tablespoonful.

Hypophosphites.—Various combinations of *hypophosphorous acid* with a mineral basis and with alkaloids have been largely used as tonics and reconstructives in the debility of *phthisis*, *neurasthenia*, and allied conditions. In our experience these combinations have seemed to exert no other influence in disease than that of their active bases. According to the researches of Paquelin and Joly and of A. Boddaert,[12] the hypophosphites are rapidly eliminated through the kidneys in an unchanged condition. Boddaert affirms, on what we believe to be insufficient evidence, that they increase distinctly the elimination of urea, of phosphorus, and of chlorine. SYRUPUS HYPOPHOSPHITUM, U. S. (*Syrup of the Hypophosphites*), contains the hypophosphorous salts of calcium, sodium, and potassium. Of this syrup or of the SYRUPUS HYPOPHOSPHITUM CUM FERRO, U. S., two fluidrachms (7 C.c.) may be given after meals.

COLCHICI SEMEN—COLCHICUM SEED. U.S.
COLCHICI RADIX—COLCHICUM ROOT. U.S.

Colchicum autumnale, or *meadow saffron*, whose products the above drugs are, is a little plant growing in Continental Europe and in England. It is not really the root that is official under the name of colchicum root, but the thickened swollen end of the stem, with the little bulblet whose office it is to develop a new plant. This *corm* is solid and fleshy, an inch and a half to two and a half inches in length, with a longitudinal groove, having a nail-like process (the bulblet) at its base. In the shops it is very commonly kept in transverse slices, which are notched and cordate; the taste is bitter, hot, and acrid. Colchicum seeds are nearly round, about an eighth of an inch in diameter, and of a bitter, acrid taste. The active principle of both seed and corm is an alkaloid, *Colchicine*.*

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* The active principle of colchicum is without doubt colchicine. See Geiger (*Annal. Chem. Pharm.*, vii. 274), Hoppe, Aschoff (*Vierteljahresschrift f. Prakt. Pharm.*, vi.), Schroff (*Oester. Zeitschrift f. Prakt. Heilk.*, 1856), and Albers (*Deutsche Klinik*, 1856, xxxvi.). Jacobi affirms that absolutely pure colchicine is physiologically inert, but that it is transformed in the system into a brown, amorphous, oxidation product, *oxydicolchicine*, which produces the poisoning symptoms commonly attributed to colchicine. In regard to the activity of colchicine, Mairet and Combemale (*Comptes-Rendus*, civ. 515) find that if given by the stomach it causes when in the dose of 0.0002 gramme per kilogramme in the lower animals no diarrhœa, but polyuria; of 0.00025 gramme per kilogramme, violent purgation, with a little general depression; of 0.000476 gramme per kilogramme, violent bloody diarrhœa, with salivation, polyuria and great feebleness, lessening of the temperature, and rapid respiration. Given hypodermically, the diuretic dose is 0.00015 gramme, the purgative dose 0.00025 gramme, and the toxic dose 0.00035 gramme per kilogramme. When given to the healthy man by the mouth it produces in doses of 0.0002 to 0.003 gramme mild headache, muscular weakness, abdominal pains, increased frequency of the pulse, thirst, and increased diuresis; in doses of 0.005 gramme, diarrhœa and diminution of the urine.

Colchiceine is a neutral crystallizable substance, soluble in water, which is produced

Local Action.—Absorption.—Elimination.—Although preparations of colchicum brought in immediate contact with the mucous membrane do not seem to be immediately and actively irritant, yet when taken internally they produce violent gastro-intestinal irritation which is probably closely connected with attempts at elimination. Concerning the elimination of the active principle of the drug we have little knowledge, although it can scarcely be gainsaid that the alkaloid escapes with the urine and, when in toxic dose, probably more largely with the gastro-intestinal secretions.

General Effects.—The smallest therapeutic doses of colchicum produce no distinct symptoms. After somewhat larger amounts there is gastro-intestinal disturbance, as shown by abdominal uneasiness, colicky pains, borborygmi, loss of appetite, moderate purging, and sometimes nausea,—symptoms differing in degree only from those of poisoning by the drug. Before these come on, however, there is a lowering of the pulse-rate, sometimes as much as twelve beats per minute, which, according to some authorities, is sometimes accompanied by free diaphoresis, though it has never been our experience to see this symptom. Any nervous symptoms, such as vertigo, headache, or muscular weakness, which may be present as the result of the administration of colchicum are probably sympathetic from the gastro-intestinal irritation.

In poisonous doses colchicum produces violent purging, whose onset is soon followed by severe, often uncontrollable, vomiting. The discharges from the bowels are at first large and serous, but later become smaller, more mucous, with flaky deposits, and finally in some cases bloody. Abdominal pain may be absent or present, but if present is generally griping ; sometimes there is gastric burning. Nervous symptoms have been prominent in some of the severe cases. In one instance, it is said, a feeling of numbness or prickling was complained of by the patient ; but this seems not to be common. Spasms are very frequent, and sometimes convulsions, which may be fatal, are present. Muscular pains are not rarely experienced : in some cases replacing the spasms, and probably in all other cases coincident with them, is

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by the action of mineral acids and certain other agencies upon colchicine. Its toxic influence has been studied upon dogs by Samuel R. Percy (*Amer. Med. Times*, April, 1862, 167), according to whom it produced symptoms very similar to those caused by colchicine ; they are—increase in the frequency of the pulse, severe purging with tenesmus, vomiting, finally great slowing of the pulse and failure of the heart's action, and death without convulsions. The urine, at first increased, was afterwards suppressed. On post-mortem examination, the mucous membrane of the intestines was found highly inflamed, that of the stomach slightly so, and the heart and arteries were filled with black tarry blood, similar to that of colchicine-poisoning. On the other hand, Paschkis asserts that one and a half grains of colchiceine injected into the jugular vein of a dog produced no results whatever. It is evident that the two experimenters had different substances. Ferrer (*University Med. Mag.*) found that colchiceine acts chiefly upon the motor, and not, as does colchicine, upon the sensory nerves, and that whilst it stimulates the peripheral vagi, it does not depress the heart-muscle.

S. R. Percy affirms that in gout colchiceine increases the elimination of urea and of uric acid, but his experiments are too few to be decisive.

great muscular weakness, amounting, as death approaches, to paralysis. Finally, a condition of collapse develops, the circulation fails more and more, the pulse, which has been frequent and feeble, becomes rapid and thready, the skin cold, pale, or livid, and bedewed with sweat, and death from exhaustion results. Consciousness is preserved until the last. The effect of lethal doses of colchicum on the urinary secretion varies: sometimes the kidneys seem to be nearly unaffected almost to the last; sometimes their functional activity is decidedly increased, but in other cases it is diminished, and even suppression of urine has been noted.

After death from colchicum the blood is generally found very dark and imperfectly coagulable, but whether this is due to a direct action of the poison or is the result of the slow death by asphyxia and exhaustion has not been determined. The chief changes are, however, in the alimentary canal, the mucous membrane of which is much swollen, intensely congested, sometimes ecchymotic, or with blood free in the intestine.

Upon most animals colchicum acts very much as it does upon man, in poisonous doses producing, as prominent symptoms, severe and often bloody purging, vomiting, great prostration, embarrassed respiration, finally more or less pronounced paralysis, and death, not rarely preceded by convulsions. Reflex actions are lessened and finally abolished (Albers,[1] Rossbach[2]) in the frog; but Rossbach affirms that there is a precedent stage of convulsions with excessive reflex activity; in warm-blooded animals this first stage of excitement is rarely, if ever, seen.

As colchicum is rarely used in medicine except in such doses as produce no sensible general physiological action, being in fact employed as an alterative,—*i.e.*, to affect disease conditions in some unknown way by its continuous administration,—it is plain that its physiological action should be studied from two points of view: first, that of the large poisonous dose; second, that of the continuous small dose. In regard to the action of toxic doses there is some contradiction on the part of experimenters. Rossbach and Adolfo Ferrer y Leon[3] are in accord in affirming that the drug has so little influence upon the circulation that any alteration which occurs in its poisoning is probably secondary; whilst Schaitanoff and Paschkis[4] state that the drug notably increases the arterial pressure. In the elaborate experiments of Rossbach the motor nerves and the striated muscles were not affected by the poison, but the higher nerve-centres, the spinal cord, and the peripheral sensory nerves suffered palsy. The depressant action of the poison upon sensibility has been confirmed by Paschkis, whilst Ferrer y Leon determined that the sensory nerves are especially affected, his results in this respect being concordant with those of Rossbach. According to Rossbach, the pneumogastrics are not affected until near death, whilst the splanchnic nerve and the intestinal fibres of the vagi escape altogether. Paschkis, on the other hand, states that the normal relations of the intestinal peristalsis with the pneumogastric nerve are destroyed by colchicine.

In contrast with this discord is the universal testimony by experi-

menters that the force of the poison is chiefly expended upon the alimentary canal, which is always found, at least in mammals, to be in a condition of intense inflammation, even when colchicine has been given hypodermically.

The relief which is afforded in a gouty condition by purgative doses of colchicum can readily be explained by the supposition that the drug causes the elimination of gout-poisons through the bowels, because the effects produced by doses too minute to act upon the gastro-intestinal tract are often decisive ; so that great interest attaches to the question as to the influence of the drug upon the kidneys. It is certain that sometimes the continuous moderate use of colchicum distinctly increases the flow of urine, but its action is not invariable, and, unfortunately, the question as to whether the drug notably increases the elimination of solid materials from the urine cannot at present be answered with definiteness, the testimony in regard to the action of colchicum upon the elimination of urea and uric acid in health and in disease being too contradictory and insufficient to warrant any conclusion.

Thus, Bird[5] quotes Krahmer's experiments as showing that colchicum does not increase the amount of solids eliminated in health, and intimates that his own investigations had given similar results ; whilst Hammond,[6] on the other hand, in a series of experiments in which every care to avoid fallacies, by maintaining equality as to diet and exercise, was observed, found that while squill and digitalis increased only the watery part of the urine, both the organic and the inorganic solids were remarkably augmented by colchicum.

The testimony as to the effects of the drug in disease is no less discordant. In 1828 Chelius announced that during its administration in gout the amount of uric acid eliminated is nearly doubled. R. Lewins[7] submitted the urine of several persons suffering from gout, taken before and after the administration of colchicum, to Christison, who found in the colchicum-urine the *proportion* of urea nearly double, and that of uric acid greater than, that of the other specimens.

In 1852 Maclagan[8] analyzed the urine of three cases of rhematism before and after the exhibition of colchicum : in two instances the *proportion* of urea was very greatly increased, that of uric acid slightly so. In the third case the effect just noted happened at first, but not afterwards.

On the other hand, Stillé states that Graves and Gardner affirm that the urates diminish under the use of the medicine. It is evident that these different results are not so contradictory as they seem, for it is possible that in one case the colchicum may so act as to increase the elimination of urea, in another that of uric acid, and that when one of these is increased the other may be unaffected, or even diminished.

Further, when the medicine purges freely it is very probable that elimination by the kidneys is lessened ; and no account of this is taken by any of the observers whose original papers we have seen. Moreover, these observers also all contented themselves with noting the proportion of urea and uric acid in the urine, when it is evident that the mere proportion, unchecked by the absolute amount of urine secreted during the twenty-four hours, is no criterion as to the absolute amount eliminated. A. B. Garrod[9] has made a study of the subject in such a way as to avoid this fallacy, and found that the elimination of urea and uric acid was sometimes increased, but that, on the whole, no marked effect was produced. Noel Patton[10] states that in his experiments on dogs small doses of colchicum increased very distinctly the elimination of urea and uric acid, as well as the amount of the urine ; while large doses lessened the amount of urinary secretion and increased slightly

Between the paroxysms colchicum may steadily be exhibited to the gouty subject in small doses (ten drops of the wine of the root three times a day), and often great advantage is derived from its combination with potassium iodide. Ten grains of the iodide and ten drops of the colchicum wine may be given three times a day.

In *rheumatism* colchicum has been highly recommended, but is of little value. Colchicum has been administered in various diseases, but when there is no rheumatic or gouty taint is at present very rarely used.

TOXICOLOGY.—The symptoms of poisoning by colchicum have been already enumerated. The fatal dose varies, but is small. George B. Wood[12] states that death has been produced by two drachms and a half of the wine of colchicum root, and Taylor[13] records a case in which three drachms and a half proved fatal. On the other hand, recovery has taken place after the ingestion of an ounce.* According to the experiments of Schroff, *colchicine* is eighty to one hundred times stronger than the fresh corm. According to Heinrich (quoted by Husemann), 0.15 grain of colchicine will produce poisonous symptoms in man, and in Krahmer's[14] experiments 0.3 grain caused in an adult violent serous purging, lasting for four days, and accompanied by severe tenesmus. Casper has seen death result from a quantity of the wine containing 0.025 to 0.03 gramme (0.37–0.45 grain) of colchicine; but, according to Husemann, recovery has taken place after the ingestion of 0.045 gramme of the alkaloid.†

The treatment of colchicum-poisoning is as follows. If the stomach and bowels have not been freely evacuated, administer at once an emetic and a cathartic, so as to empty the alimentary canal; allow the patient to drink freely of warm water, to aid in these operations and to act on the kidneys. Give freely of tannic acid, as the only known chemical antidote, although experiments upon animals have shown that it is not to be relied upon. To check the vomiting and purging, administer opium freely; and to allay the irritation, cause the patient to drink freely of albuminous matter, such as white of egg dissolved in water: the tannic acid having been given as soon as possible after the taking of the poison, the demulcents are useful in the more advanced stages. Symptoms of gastro-enteritis or of collapse are to be met as they arise.

ADMINISTRATION.—Colchicum is never used in substance; the wine of the root is deservedly the most popular preparation. It has been asserted that colchicine hypodermically administered is especially effica-

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* See case in *L'Union Médicale*, Aug. 1848.

† George W. Major (*Canada Med. and Surg. Journ.*, Dec. 1873) records seventeen cases of poisoning from one bottle of wine of colchicum seeds, occurring in Montreal, seven of which proved fatal. The patients had been vomiting and purging almost continuously for many hours when first seen, and the symptoms were exactly those of the stage of collapse of severe cholera morbus. In no case was the purging bloody. Consciousness was preserved to the last, and in only one case was there anything like convulsions. There was decided numbness of the extremities, and a peculiar hoarseness of the voice was especially noted.

cious in rheumatism; the dose is one-fiftieth of a grain (0.0013 Gm.).[15]

The official preparations from the seeds are: the tincture (TINCTURA COLCHICI SEMINIS—fifteen per cent.), dose, half a teaspoonful to one and a half teaspoonfuls; the wine (VINUM COLCHICI SEMINIS—fifteen per cent.), dose, half a teaspoonful to one and a half teaspoonfuls; and the fluid extract (EXTRACTUM COLCHICI SEMINIS FLUIDUM), dose, two to six minims (0.12–0.36 C.c.).

The official preparations of the root are: the wine (VINUM COLCHICI RADICIS—forty per cent.), dose, ten to fifteen minims (0.6–0.9 C.c.); as a purgative, half a fluidrachm (1.8 C.c.); the extract (EXTRACTUM COLCHICI RADICIS), dose, one to two grains (0.06–0.12 Gm.); and the fluid extract (EXTRACTUM COLCHICI RADICIS FLUIDUM), dose, two to four minims (0.12–0.24 C.c.).

SARSAPARILLA—SARSAPARILLA. U.S.

The root of Smilax officinalis, Smilax medica, Smilax papyracea, and other species of Smilax, woody vines inhabiting Mexico and the northern portions of South America. There are in commerce a number of varieties of sarsaparilla, the two most important of which are the *Honduras* and the *Brazilian*. The former of these is almost the only sarsaparilla used in this country. It occurs in bundles two or three feet long, composed of several very long, thin roots, folded upon themselves, the whole being bound round by a number of turns of the root. The Brazilian sarsaparilla also comes in cylindrical bundles, each of which is closely wrapped about by a very flexible stem: it mostly has fewer rootlets than the Honduras variety. The crude sarsaparilla has little or no smell, but its taste, which is at first simply mucilaginous, soon becomes, if the root be chewed, persistently acrid. According to George B. Wood, the degree of this acridity is the best measure of the activity of any specimen of the drug.

There are in sarsaparilla three active glucosides,—*Parillin*, of Palotta, *Saponin*, of Otten, and *Sarsaponin*, of Schulz. To these glucosides, separate or combined, various names have been given by various investigators, such as *smilacin*, *salseparin*, *sarsaparillin*, and *parillinic acid*. The three principles belong to the saponin group, and resemble in physiological action saponin from quillaia bark. According to Kobert, sarsaponin is about the most active poison to the red blood-disks known, but is less active as a cardiac paralyzant than are most saponins. To it sarsaparilla is believed to chiefly owe any medical value it may possess. Palotta asserts that thirteen grains of parillin will cause vomiting, constriction in the throat, weakness, diaphoresis, and depression of the circulation. On the other hand, Böcker,[1] of Bonn, has exhibited it in doses of a like amount without producing any symptoms whatever. There does not seem to be reason for believing that the saponin principles, in the largest therapeutic dose, of sarsaparilla are in sufficient amount to exert a perceptible influence upon the human system.

It has been asserted that sarsaparilla acts as a diuretic and diaphoretic; but the only record we have met with of any careful experimenta-

tion is that of Böcker. That investigation seems to show conclusively that the drug has no marked influence upon the secretions. If, therefore, sarsaparilla have any value whatever in disease, it must be simply as an alterative,—as a remedy which in some unknown way modifies nutrition.

THERAPEUTICS.—Sarsaparilla has been used, and still is used, to such an enormous extent in medicine that it seems impossible to believe that it is destitute of therapeutic virtue. It is not in accordance with the plan of the present work to enter into an elaborate discussion of the recorded clinical experience with it: suffice it to say that, although the evidence is contradictory, on the whole there is a decided preponderance in favor of the value of the drug in *chronic syphilis* and in *chronic scrofulous diseases*. We have used it largely, but always in combination with more powerful alteratives, so that it is impossible to decide how much of the good achieved has been due to its influence. There are two distinct methods or objects of the use of sarsaparilla in syphilis: one as an adjuvant to mercury in the secondary stage; the other as an adjuvant to the potassium iodide, or as a sole reliance, in the advanced tertiary cases, especially where the constitution is very much broken down by the disease. It is stated that, in the latter condition, very often during its use the appetite will gradually increase, the spirits rise, the secretions become more and more normal, and the strength grow day by day.

ADMINISTRATION.—Sarsaparilla is never given in substance, but in one of the following preparations:

DECOCTUM SARSAPARILLÆ COMPOSITUM. U. S.—*Compound Decoction of Sarsaparilla.*—This is made from sarsaparilla, sassafras, guaiacum wood, liquorice root, and mezereum, and is an imitation of the famous *Lisbon Diet-Drink*. Dose, three or four fluidounces (90–118 C.c.) three or four times a day.

SYRUPUS SARSAPARILLÆ COMPOSITUS. U. S.—*Compound Syrup of Sarsaparilla.*—This contains sarsaparilla, liquorice root, senna, oil of sassafras, oil of anise, and oil of gaultheria, and is a very popular preparation, on account of its pleasant taste: it affords the only official vehicle capable of disguising the taste of the potassium iodide. The dose of it is one to two tablespoonfuls three or four times a day.

EXTRACTUM SARSAPARILLÆ FLUIDUM. U. S.—*Fluid Extract of Sarsaparilla.*—Dose, half a teaspoonful three times a day.

EXTRACTUM SARSAPARILLÆ FLUIDUM COMPOSITUM. U. S.—*Compound Fluid Extract of Sarsaparilla.*—This contains sarsaparilla, liquorice root, sassafras, and mezereum. The dose is a teaspoonful.

GUAIACI LIGNUM—GUAIAC WOOD. U.S.
GUAIACI RESINA—GUAIAC RESIN. U.S.

The heart-wood of Guaiacum officinale and of Guaiacum sanctum: the resin of Guaiacum officinale, a large tree growing in the West Indies. Guaiac wood, or *lignum-vitæ*, is imported in billets, but very generally is kept in the shops in the form of raspings or shavings. It is

a very dense wood, having a dark olive or brownish-green color. It is inodorous, but becomes somewhat fragrant when rubbed or heated. Besides the resin, its extract is believed to have medicinal properties.

Guaiac occurs in irregular lumps or masses, of a dark reddish-brown or greenish color externally, offering a conchoidal fracture with somewhat translucent edges. The odor is feeble, peculiar, agreeable, increased by heat. The taste is at first very slight, but, as the resin melts in the mouth, becomes very acrid and persistent. It is an exceedingly complex body, containing three acids, the *guaiaconic acid* of Hadelich, the *guaiac acid* of Righini, and the *guaiacresinic acid* of Hlasiwetz, besides *guaiac yellow*, a peculiar resin, and other substances. Landerer asserts that he has found in it a peculiar crystallizable substance, which he calls *guaiacin*.

When a lump of guaiac is freshly broken, it offers a dark, blackish surface, which on scraping or bruising becomes yellowish; on exposure, the well-known greenish tint is acquired, owing to a spontaneous oxidation. The ease with which the resin undergoes oxidation is its most distinctive characteristic. As already stated, the change occurs on simple exposure to the light. According to Wollaston, it is most rapid and perfect in the focus of the violet rays of the spectrum, while in the focus of the red rays the original color is regained. Oxidizing or ozonizing agents, such as nitric acid, chromic acid, iodine, bromine, and chlorine, produce this oxidation very rapidly, the resin acquiring an intense blue color.

PHYSIOLOGICAL ACTION.—Guaiac is believed by some to act as a diaphoretic, and to do good by increasing elimination through the skin. When taken internally, no sensible effect results, unless the dose be so large as to irritate the stomach.

THERAPEUTICS.—Guaiac has been very largely employed in *chronic syphilis*, in connection with sarsaparilla; also in *subacute* and *chronic rheumatism*. William Murrell* states that in doses of ten to thirty grains (0.6–2 Gm.), the resin given in electuary is very useful as an antirheumatic laxative in various diathetic affections, such as *sciatica*, *tonsillitis*, *chronic rheumatism*, etc. The dose of the simple (TINCTURA GUAIACI—twenty per cent., U. S.) or of the ammoniated (TINCTURA GUAIACI AMMONIATA—twenty per cent., U.S.) tincture is from one to two teaspoonfuls (4–7 C.c.), administered, preferably in milk, three or four times a day.

MEZEREUM. U. S.—*Mezereon* is the bark of the Daphne mezereum and of other species of Daphne, native shrubs of Europe. It is a thin, grayish, tough, flexible bark, occurring in long strips folded upon themselves, nearly odorless, but having a very acrid taste. It contains a neutral, crystallizable, bitter glucoside, *Daphnin*, besides a volatile acrid principle. Mezereon is intensely irritant, and its ointment (UNGUEN-

* *Med. Press and Circular*, November, 1890.

TUM MEZEREI) is used as a stimulant dressing to very indolent *ulcers* and to keep blisters sore or maintain *issues*. Internally, in small doses it is believed to be an alterative, but is never used except in combination with sarsaparilla. In overdoses it is an active poison, producing severe vomiting, purging, and gastro-intestinal inflammation. Sometimes the symptoms of the poisoning are simply those of collapse, with unconsciousness and other nervous disturbances, such as are seen in children from intense gastro-intestinal irritation.*

JAMBUL.—The bark of the Eugenia jambolana, an East Indian tree, has long been used in India as a stomachic astringent in *diarrhœa* and as a specific in true *diabetes*. Its active principle has not been determined, but appears to be present in the bark, in the seeds, and also in the rind of the fruit ;[1] neither have we detailed knowledge as to the physiological action of the remedy. Thomas Christy[2] found that when sufficient diastatic matter was mixed with fifty grains of starch to convert forty-five per cent. of the latter in fifty minutes into sugar, the addition of twenty-five grains of powdered jambul seeds reduced the conversion of the starch eighty-eight per cent. In Binz's[3] experiments, in dogs rendered diabetic by phloridzin, according to the method of Von Mehrung, the exhibition of jambul reduced the excretion of sugar from fifty to ninety per cent. without producing any evidences of poisoning.

Clinical reports indicate that in some cases of glycosuria jambul exerts a powerful influence for good, and we have seen the sugar entirely disappear from urine under its influence. On the other hand, it has usually failed to produce this effect, and it is not possible at present to give any reason for this difference of action ; but as no cases of poisoning or disagreeable results from it have been reported, the drug is worthy of full trial in almost any case of glycosuria. The fluid or solid extract of the bark, fruit, or rind of the fruit may be used. The commencing dose of the fluid extract of the bark may be considered to be ten minims, three times a day, rapidly increased to half a drachm (0.6–2 C.c.) or more if no result follow. Vix gave about ten drachms (37 C.c.) a day of the extract made from the rind of the fruit. In some of his cases this dose produced violent diuresis.

TARAXACUM. U. S.—The root of the common dandelion, Taraxacum officinale, is believed to have the property of altering the action of the liver, although no effect is to be witnessed from a single dose of the drug, however large,—other, at least, than some nausea. Diuretic properties have also been ascribed to taraxacum ; but the only evidence brought forward to establish this is the vulgar name which the plant bears both in English and in French. If taraxacum be useful at all, it is in cases of *dyspepsia* in which there is habitual torpor of the liver, with

* Case, *Brit. Med. Journ.*, 1882, ii. 521.

costiveness. It must be given very freely and continuously for weeks before any good effect is to be looked for. Dose of the fresh juice extract (EXTRACTUM TARAXACI, U. S.) or of the fluid extract (EXTRACTUM TARAXACI FLUIDUM, U. S.), one to two drachms (3.7–7.4 C.c.), administered after meals.

ICHTHYOL.

Ichthyol is a substance first prepared by Schroeter by the distillation of a peculiar bituminous sulphurous mineral obtained from the deposits of fossil fish. It occurs in commerce in the form of *sodium ichthyo-sulphate* and *ammonium ichthyo-sulphate*. Ammonium ichthyol is a reddish-brown, clear, thick liquid, of a hot bituminous taste and smell, at a high heat burning without ash, making with water a clear, reddish-brown solution of a weak acid reaction, which, when treated with hydrochloric acid, yields a dark resinous precipitate. Sodium ichthyol is a dark, tar-like substance of an alkaline reaction, perfectly soluble in water. Both these preparations combine with fat and vaseline in all proportions. The ichthyol preparations are said to contain ten per cent. of sulphur.

THERAPEUTICS.—According to Baumann and Schotten, ichthyol has little apparent action on the general system, and when given to dogs in doses of five drachms produces no symptoms save diarrhœa. As a local remedy it has been extravagantly praised by Unna, Kiesner, and a large number of German dermatologists and surgeons, and has also received strong encomiums in America. When applied freely in a pure form to the sound skin it produces slight irritation and burning. It is asserted to have, when used as a local application, peculiar alterative properties, and also the power of penetrating through the skin so as to be able to act as an alterative anodyne and discutient in diseases not only of the skin but also of the subjacent tissues, probably having also germicidal powers. The cases in which it is of value are characterized generally by inflammatory enlargement or inflammatory pain.

In various skin diseases ichthyol has been used with alleged remarkable results,—in chronic *eczema*, chronic *urticaria*, *acne*, *intertrigo*, *lupus*, *keloid*, etc. In *lepra* Unna combines its internal and external use (dose, fifteen grains (1 Gm.) a day). It has also been recommended in the strongest terms for the relief of various *ulcerations* of the *skin* and for the prevention of *pitting in small-pox*, and also in *erysipelas*. In *lumbago* and other forms of *muscular rheumatism*, in *rheumatic* or *gouty joint disease*, indeed, in almost every form of subacute or chronic *gout*, according to Schweninger, Lorenz, and others, a few rubbings with pure ichthyol or a fifty per cent. ointment will produce an immediate and remarkable effect. It has been largely used in the treatment of *sprains*, *contusions*, *burns*, and *frost-bites*. If one-half that has been said of it be true, it is a local remedy of extraordinary power and value. Schmidt has even seen it soften and disperse a *lipoma*, and D. Hayes Agnew commends it very highly in the treatment of recent *lymphatic enlargements*.

We have used it in sprains with apparently some relief. When the skin is intact and not irritated, the ichthyol itself or a fifty per cent. ointment may be employed. In *erysipelas* Von Nussbaum covers the affected part, after thorough disinfection, with a thick layer of equal parts of ichthyol and vaseline, and this in turn with a thick layer of salicylated cotton. The result is said to be immediate, the disease disappearing in a single day. In various skin diseases and ulcerations the strength of the application may vary from one to fifty per cent. Lorenz affirms that in acute *coryza* and inflammations of the nose or mouth a mixture of one to ten per cent. of ichthyol and vaseline is very efficacious. Both Unna and Lorenz deny that it has any antiseptic properties.

Ichthyol Albuminate.—Ichthalbin is a greenish-brown powder, made by precipitating albumin with ichthyol, and containing seventy-five per cent. of ichthyol. It is insoluble in water, but soluble in alkaline solutions; it is odorless, almost tasteless, and has been highly praised in *syphilis* and in *scrofulous* conditions with lowered general nutrition. Dose, fifteen to thirty grains (1–2 Gm.) three times a day.

NUCLEINS.—An organic remedy whose value is very problematical is the so-called neuclein, or nucleins. Originally the term nuclein was applied to a peculiar phosphorized substance isolated from the nuclei of pus-cells. Later clinical research has shown that there are in nature numerous closely allied, phosphorized, proteid-like bodies to which the name may be applied, and which have been shown by Kossel and his coworkers to be a combination of nucleic or nucleinic acid with a proteid body. Nuclein on a large scale is preferably prepared from the yeast-cell, and readily yields *nucleic acid*, an amorphous white powder of strong acid reaction, readily soluble in alkalized water, containing as much as nine per cent. of phosphorus, but, according to Chittenden, no proteid matter. It rarely exists free in animal cells, as in spermatozoids, but is generally united with a proteid. Nuclein is furnished to commerce especially in the form of a five per cent. solution, of which the dose is from ten to sixty minims hypodermically. It is alleged that it is a powerful germicide, and so slightly toxic that it has been injected intravenously by Vaughan and McClintock until the blood of the animal contained one and one-eighth per cent. of pure nucleic acid without serious results. It has been especially commended in the treatment of *tuberculosis*, *puerperal fever*, and other germ diseases.

ANIMAL DRUGS.

There have recently come into use in medicine certain substances derived from animal tissues which have the property of widely affecting nutrition in the human body, and which probably may be more appropriately considered under the head of Alteratives than in any other of the classes included in the scheme of the present volume. From time imme-

morial animal tissues or their derivatives have been used in the treatment of various diseases, and this custom has survived in the so-called isopathic branch of homœopathy and among Chinese and other barbarians. There is no scientific reason, nor yet any good clinical observation, to show that most of these substances act therapeutically in any other way than by making a psychical impression. On the other hand, there has recently arisen a method of using certain animal substances in the treatment of disease which rests upon a scientific basis, and is continually making a record of increasing triumphs. Two classes of these substances claim attention: in the first class are included certain organs which have often been spoken of as ductless glands, of obscure anatomy and more obscure function, which are in some way connected with the general bodily nutrition; in the second class are contained certain substances which are formed in the animal organism during infectious diseases, and have the power in some way of fortifying the system against the germs of these diseases.

Besides these two classes there are some animal substances whose physiological and therapeutic value is very doubtful, but whose recent employment in medical practice has been so wide-spread as to forbid their being passed by in complete silence.

Extracts of the *bone-marrow* and of the *spleen* have been used in the treatment of *leucocythæmia*, but so far there has been no great success, and the reason of the failure is obvious when we remember that in leucocythæmia the bone-marrow and the spleen are hypertrophied, not atrophied. When there is an excess of white corpuscles, it is not probable that glycerin extracts of marrow will prove valuable, since there is already too much marrow activity. In *pernicious* and other *anæmias* extract of bone-marrow has been employed by Frazer, Hamilton, J. S. Billings, Jr., and others, with varying results. All that can be said at present is that there is sufficient evidence to warrant the administration of the medullary glyceride in cases of severe anæmia, although the probabilities of doing good are not great.

There have been used and much advertised as valuable in diseases of the respective organs various animal extracts, *cerebrine* from the brain, *cardine* from the heart, and so on. The most plausible theory explaining how these substances are of value in medicine is that every organ takes something out of the blood for itself and thereby leaves the blood more pure and free from substances which are deleterious to other organs. There is no probability of truth in this theory, and no known reason why extract of brain should have any influence on the brain, or extract of heart upon the heart, neither of these organs having any known direct connection with nutrition.

It is somewhat different with Brown-Séquard's famous *elixir of testicles*. As we know, the genital glands hold some relation to the general nutrition. Their removal early in life modifies the whole physical and moral character of the animal, and, therefore, *a priori*, it is possible that there might be obtained from them a substance which would have some effect

upon nutrition ; it is, however, during the developmental period only that these glands are active in their relation to nutrition, and clinical results have not confirmed the assertions of Brown-Séquard as to the aphrodisiac and general stimulant powers of his elixir, which is to-day rarely used. John B. Shober asserts that the *mammary gland* has an influence on the uterus, and affirms that he has derived benefit from its use in *fibroid tumors* and *menorrhagia*.

DUCTLESS GLANDS.

The so-called Ductless Glands, which may on occasion be used with advantage as remedial agents, are the thyroid body, the suprarenal capsules, and perhaps the thymus gland and the spleen.

THYROID BODY.

The exact function of the thyroid body is not definitely known ; the removal of it causes death in both dog and man. In the dog the lethal result takes place in the midst of tetanoid symptoms, death occurring usually during a convulsion. In man its absence, congenital or operative, produces the disease known as *myxœdema*, first described by Ord ; the symptoms of this disease are increasing weakness associated with swelling of the body, enlargement and thickening of the skin, mucoid exudation into the subcellular tissue, and a very extraordinary slowing of all functions. The appetite is feeble, the movements are slow, the temperature is subnormal, and the patient thinks with great slowness ; as the days go on the universal slowing of function becomes more and more marked until the subject sinks into a condition of complete apathy with very much lowered temperature and a failure of all vital activities.

Baumann[1] isolated from the thyroid gland a proteid substance containing iodine, which he asserted to be the active principle of the body. The activities of this substance, which is variously known as *thyroiodin* or *iodothyrin*, have been called in question by Gottlieb[2] and Wormser,[3] who state that it is incapable of stopping the progress of symptoms caused by thyroidectomy. But the contrary results achieved by E. Roos,[4] Arthur Hennig, Treubel, Ewall, E. Levy,[5] Hildebrandt,[6] and Baumann and Goldmann[7] seem to confirm the claims of Baumann ; and even if the substance be not the sole active principle of the gland, much therapeutic virtue must be conceded to it. *Thyreoantitoxin*, which was described by Fränkel,[8] contains no iodine, and appears not to be active (Roos) ; a statement which is also true of the principle separated by Drechsel. (See Robert Hutchinson.[9]) It would appear probable from the various researches that thyroiodin is the chief active principle of the thyroid body, but that there is also in that body a second substance which has physiological activity.

Physiological Action.—In elaborate experiments of G. Ballet and E. Enriquez[10] upon dogs it was found that half an hour to two hours

after the ingestion of a full meal of the sheep's thyroid there was usually elevation of temperature, with great increase of the pulse-rate, though in some cases the tachycardia alone developed. Rarely there was general excitement with paroxysms of violent tremblings and dyspnœa. The subcutaneous injection of the extract of the thyroid caused immediate fever, tachycardia, crises of trembling and dyspnœa, extreme agitation, and in two cases distinct exophthalmos. Continuous thyroid-feeding produced conjunctivitis, general wasting, and derangement of the digestion, but in no case death. On the other hand, repeated hypodermic injections of the extract led to rapid emaciation, paroxysms of violent diarrhœa and of melanæmia, sometimes polyuria, sometimes albuminuria, with great weakness of the hind legs, occasionally amounting to paralysis, followed by torpor, collapse, and death. Tumefaction of the thyroid lobes was noted in some cases during life, and after death the thyroid body was found to be greatly enlarged and mottled with ecchymoses. By microscopic examination there were revealed marked evidences of inflammatory change in the thyroid gland, with destruction of the alveolar and epithelial cells and the development of sclerotic tissue.

In man *thyroidismus*, so called, has been developed in a number of cases by the excessive administration of the gland. The chief symptoms are progressive loss of weight, shortness of breath, weak, rapid pulse, and general nervousness.

As the result of his own experiments, Hertoghe[11] asserts that the thyroid extract lessens the activity of the pelvic organs of women, whilst it stimulates the thoracic genital organs, so that it causes arrest of menstruation but increases the secretion of milk.

According to Ott, the drug depresses reflex action in the frog.

Circulation.—Vamossy and Vas[12] state that the intravenous injection of iodothyrin has no effect on pulse-rate, blood-pressure, or respiration, and attribute the symptoms seen after its ingestion entirely to disturbances of metabolism. But Haskovec,[13] Oliver and Schäfer,[14] and Ott[15] agree that the thyroid extract causes a slight fall of pressure, with some increase in pulse-rate, which, according to Haskovec, is not prevented by section of the vagi. Cyon[16] says that iodothyrin increases the excitability of the vagus.*

Respiration.—Ott found the *respiratory* rate increased in the rabbit by iodothyrin.

Blood.—According to Vamossy and Vas, and Bell,[17] the thyroid extract has practically no effect on the red blood-corpuscles or hæmoglobin. M. L. Perry[18] found, as the result of thyroid-feeding in the insane, no change in the number of the white blood-corpuscles, but a marked lessening of the percentage of the multinuclear and a corresponding increase of the mononuclear leucocytes, results which agree substantially with those of

* His paper is a preliminary communication, and details no proofs of his rather remarkable assertion that iodothyrin sets aside the vagal palsy produced by atropine.

Mosely,[19] save that the latter found some lessening in the total number of white corpuscles. Bell and Vamossy and Vas, on the other hand, found an increase in the number of leucocytes brought about by the thyroid body.

Nutrition.—Although Scholz,[20] Richter,[21] and Paul Mayer[22] failed to get evidences of increased nitrogenous elimination over intake, nevertheless, the concordant results of Roos,[23] Gluzinski and Limberger,[24] David,[25] Schöndorff,[26] Napier, Mendel, Ord, and others leave no room for doubt that there is an increase in the destruction of proteid substances under the influence of thyroid-feeding. Roos found that there is not only an increase in the excretion of nitrogen but also in phosphorus and chlorides. Irsai, Vas, and Gara[27] have shown that these facts hold true in goitrous, and Vermehren in myxœdematous subjects.

But the loss of weight is not entirely due to the destruction of albuminous tissues ; thus, in Schöndorff's experiments, out of 2.2 kilos lost in a three weeks' experiment, there was only sufficient increase of nitrogen excreted to account for one kilo of bodily tissues. Bleibtreu and Vendelstadt attribute only one-sixth of the weight-loss to the breaking down of the proteids. The conclusion seems, therefore, inevitable that there must be under the influence of thyroid-feeding not only increased nitrogenous katabolism, but also destruction of the fatty tissues. This conclusion is confirmed by the results of Magnus-Levy,[28] who found an increase in the absorption of oxygen and giving off of CO_2 brought about by thyroiodin. In myxœdematous subjects the increase in the demand for oxygen may amount to ninety per cent. Magnus-Levy found Fränkel's thyreoantitoxin to be without effect on the exchange of gases. Schöndorff[29] states that the destruction of nitrogenous tissues does not begin until the store of reserve fat is exhausted.

Bettmann[30] and W. D. James[31] report *glycosuria* following free use of the thyroid treatment.

THERAPEUTICS.—It is evident that a myxœdematous condition of the body is the result of the absence from the blood of some principle or principles which are supplied in the normal animals by the thyroid gland, and which may be furnished to the blood by feeding with thyroid glands. It is further apparent that the myxœdematous patient who has been relieved by such artificial supply must relapse when the supply is cut off ; so that treatment of a *myxœdema* consists of two stages : first, that in which large amounts of the gland are administered in order to remove the results which have been produced by the lack of the thyroid principle ; second, the protracted stage of convalescence in which small doses of the gland are given continuously in order to prevent the recurrence of the myxœdemic symptoms.

The destruction of fatty tissues under its use would seem to render the drug of great value in *obesity*. Unfortunately, however, the system soon becomes accustomed to it, and although there is nearly always temporary benefit in properly selected cases of obesity (see page 20), the

patients are very apt to relapse, even despite the continued use of the drug.*

The diseases in which the thyroid body has been given include nearly all the chronic and many of the acute troubles known to humanity. In some of them it has seemed to be of benefit, but in most has proved useless.

In various forms of *skin disease*, especially *psoriasis* (Bergmann[32]), it has been recommended. It has even been asserted to be of value in *lupus* (Gould[33]).

In mental disturbances, such as *melancholia* or *idiocy*, not dependent on myxœdema, it may be tried, although the reported results (Bell, Dobrowsky[34]) are not brilliant, and our own trials have been an unbroken series of failures.

The recorded trials of it by Hertoghe and by Mosely in uterine troubles indicate that it will prove of service in *menorrhagia*, *endometritis*, and kindred disorders. Diaballa and Illyés[35] report its use in a case of *nephritis* with increase of the quantity of urine and urea and diminution of the amount of albumin.

Very interesting is the report by R. Lépine[36] of a case of progressive *myopathy*, in which muscles not very badly involved so improved that the patient, who had taken sixty grammes a week of the fresh gland, returned to his work, refusing to stay longer in the hospital.

In *simple goitre*,—the goitre of Switzerland,—before calcareous degeneration has taken place, thyroid treatment will often cause destruction and absorption of the overgrown gland. The extract has been used by J. William White with asserted excellent results in bringing about the absorption of large contracting cicatricial masses which resembled true *keloid*. It has been employed in old syphilitic and other *leg ulcers*, and may be cautiously tried in almost all forms of disturbed nutrition not attended by a tendency to emaciation.

In any case the occurrence of symptoms of thyroidism should be the signal for the lessening or withdrawal of the dose. In *exophthalmic goitre* the extract is *a priori* contra-indicated, the most probable explanation of the symptoms of the disease being an excess of the thyroid principles in the system, and in several cases in which we have tried it it has very distinctly aggravated the symptoms. It would also seem to be contra-indicated in *diabetes mellitus*.

ADMINISTRATION.—The thyroid gland may be given raw or very slightly boiled, to the amount of a quarter to half of the gland of the sheep daily. The glycerin extract or the dried and powdered gland is, however, thoroughly efficient and may preferably be used. A grain of the dried gland may in the beginning of the treatment be exhibited three times a day, the dose being increased until fifteen or twenty

* See Grawitz (*München. Med. Woch.*, 1896, 43, 312), Mathieu (*Gaz. de Hôp.*, Paris, 1896, 69), and Yorke Davies (*Brit. Med. Journ.*, 1894, ii. 42); favorable.

grains (1–1.3 Gm.) a day are taken, or some nervousness, shortness of breath, rapid pulse, or other physiological symptoms are produced. The dose of iodothyrin is about the same as that of the dried gland (fifteen grains).

SUPRARENAL CAPSULES.

It has long been known that the so-called Addison's disease, which is characterized by a progressive asthenia, a peculiar bronzing of the skin, anæmia, and loss of digestive power, with excessive vomiting, results from atrophic or destructive disease of the suprarenal capsules, but the immediate cause of the symptoms has never been satisfactorily explained. In 1895 Oliver and Schäfer[1] and Szymonowicz and Cybulski[2] published almost simultaneously papers demonstrating the extraordinary effects of these bodies on the circulation. Since this a large amount of work has been done towards isolating the active principle of the suprarenal bodies. Oliver and Schäfer showed in their first communication that the physiological activity of the gland resided in the medulla, and have since been confirmed by numerous observers. Vulpian observed as early as 1856 that the suprarenal medulla gives a blue color with ferric chloride ; and Langlois[3] has proved that the intensity of this reaction is in direct proportion to the physiological activity of the body. On account of this and other chemical reactions the active principle has been supposed to be pyrocatechin or some closely allied substance. In 1897, however, Abel[4] obtained from the suprarenal bodies, by precipitation with benzoyl chloride and sodium hydrate and separation with sulphuric acid, the benzoate of a substance , not pyrocatechin, which he classed among the alkaloids. Since then Abel[5] has succeeded in preparing several salts of this principle, for which he proposes the name *epinephrin*, and determined the percentage formula for the base to be $C_{17}H_{15}NO_4$, but has not yet been able to separate the pure base. The salts, however, are exceedingly active, a dose of 0.000018 gramme (about one-three-thousandth of a grain) per kilo of body-weight producing distinct effect upon the blood-pressure.

Dreyer[6] found the active principle of the suprarenals in the vein coming from the suprarenal capsule, and that stimulation of the splanchnics increased the amount present in the blood. From these experiments it would seem that the active principle is a true glandular secretion. This is confirmed by the observation of Pettit,[7] that the adrenals are affected by glandular poisons, as pilocarpine, in the same manner as are the other glands of the body.

Langlois concludes from his experiments that there must be more than one active substance in the gland ; a view which is also adhered to by Corona and Moroni.[8] It would seem that one of the functions of the glands is to destroy toxic substances. Thus, it seems established that the adrenal bodies contain a considerable amount of neurin, a toxic substance resulting from katabolism of nervous tissue, and that this substance appears in the urine of persons suffering from Addison's disease ; and

Albanese has shown that animals are less resistant to neurin after extirpation of their adrenals. Boinet[9] (confirmed by J. E. Abelous[10]) has found that this applies also to atropine and nicotine. Langlois and Charrin[11] discovered that the repeated injection of certain toxins in sublethal doses produced an hypertrophy of the suprarenal capsules; but that instead of being physiologically more active, such hypertrophied glands lose their reaction towards ferric chloride and also their effects on the blood-pressure. The fact that the hypertrophied glands affect the circulation less is very strong evidence that the circulatory poison is not the same principle as the antitoxic substance.*

PHYSIOLOGICAL ACTION.—*Local Action.*—Locally applied, the extract of the suprarenals acts as a powerful constrictor of the blood-vessels. It has of itself no local anæsthetic properties, but when used in conjunction with cocaine, enhances the powers of that drug, probably by its action on the blood-vessels.

Elimination.—The active principle of adrenals is very rapidly destroyed or eliminated in the system, since the effects do not last much over ten or fifteen minutes. Cybulski discovered that the urine of animals poisoned with suprarenals is capable of producing a rise in the blood-pressure, and therefore believed that the active principle is eliminated by the kidneys. Langlois,[13] however, found that maceration with the liver destroyed the active principle of the gland, that ligation of the hepatic vein prolonged the duration of its effect, and that when injected into the portal vein the suprarenal had comparatively small influence upon the circulation. He therefore comes to the conclusion that it is largely oxidized in the liver.

General Effect.—The most manifest action of suprarenal bodies is upon the circulation, so that after the exhibition of anything like the therapeutic dose the only symptoms produced are connected with the circulation.

Toxic doses of the extract cause in the frog progressively increasing loss of power without a true paralysis, and death apparently through an asthenic failure of respiration; in mammals a rapid and extreme enfeeblement, with failure of respiration and also of the circulation, consciousness being preserved very late in the poisoning. The death is apparently caused by asthenic failure of respiration, though when this function is artificially maintained there is finally loss of heart-power with paralysis of the vagi (Gourfein). No lesion except pulmonary congestion has been discovered after death.

Nervous System.—We have no knowledge as to the influence of suprarenal extracts upon the cerebrum. The failure of respiration caused by the drug is probably due to an influence upon the spinal centres, and the

* An interesting confirmation of the fact is the observation of Caussade[12] that the glycerin extract of the suprarenals when injected continuously produces an hypertrophy of the suprarenals precisely as do other toxic bodies; suggesting that the gland destroys its own secretion when in toxic amount.

general loss of power seems also to be of spinal origin, since Gourfein and Oliver and Schäfer find that after ordinary toxic doses the nerve-trunks and muscles preserve their activity up to death ; on the other hand, Vincent [14] asserts that the suprarenal extract is a muscle-poison, producing, when given to the frog in overwhelming doses, a peculiar rigidity, similar to that brought about by veratrine.

Circulation.—When to an animal the full dose of suprarenal capsules is given there is developed a slow, full pulse, followed very shortly by a great rise of the blood-pressure.* When the blood-pressure has reached its maximum the pulse becomes rapid. The slow pulse is evidently due to stimulation of the cardiac inhibitory centres, since section of the vagi prevents its occurrence. Szymonowicz and Cybulski assert that the rise of blood-pressure does not take place after section of the spinal cord, but in this they are directly opposed to Oliver and Schäfer and other experimenters. Cyon [15] found that after section of the splanchnics suprarenal capsules still caused a great increase in the blood-pressure ; and Gottlieb has shown that even when the blood-vessels are paralyzed by chloral the gland still exerts a stimulant influence upon the circulation.

In the experiments of Velich [16] there was a rise of blood-pressure not only in the arterial system but also in both auricle and ventricle on the left side of the heart. The pressure in the pulmonary artery was usually elevated, but not proportionately to the pressure in the general arterial system. The elevation in the pulmonary artery he attributes to the increased flow of blood to the right heart.

From the results of these observers it would seem that epinephrin stimulates either the muscular walls of the heart and blood-vessels or, as Gottlieb believes, their contained motor ganglia. The effects of its local application indicate that the extract does directly affect the peripheral vessels : it certainly acts upon the heart as a stimulant.

THERAPEUTICS.—There is at present considerable clinical as well as experimental evidence to show that the extract of the suprarenal capsule is of value in the treatment of *Addison's disease.* It is plain, however, that when the lesion of the adrenals is cancerous or tubercular, supplying artificially to the system an active principle prepared by those bodies cannot affect the progress of the local disease and therefore cannot bring about a cure. In various conditions of *circulatory failure* its physiological properties would seem to render it a most valuable drug. Unfortunately, the elimination of epinephrin is so rapid that it exerts but a feeble influence even when given hypodermically ; its characteristic action develops only after its intravenous injection, a method of administration which is not practicable in man until the pure active principle shall have become a commercial drug. But as a local vaso-constrictor the watery extract of suprarenals is of great value. Thus, W. H. Bates [17] and L.

* Cyon and Velich failed to obtain in many of their experiments any retardation of the pulse in dogs.

this intractable disorder. Clark[1] has found the extract of spleen useful in cases of *insanity* dependent on physical exhaustion, as in *puerperal weakness* or *anæmia*.

THYMUS GLAND.—The thymus extract was at one time used largely in *Graves's Disease*, but later experience has borne out the results of Hector Mackenzie's researches[1] that it is of no value. Fischer[2] asserts brilliant results from a saccharine extract, *pertussin*, in *whooping-cough* and all forms of bronchial troubles associated with *asthma*.

TOXINS AND ANTITOXINS.

The second class of animal substances, to which value as remedial agents must be allowed, consists of those which are the products of bacteriological growth in the animal organism. The history of the development of these substances, of their physiological activity, and of their value in the treatment of disease is of such extent that in a treatise like the present the subject cannot be thoroughly discussed; only a very brief mention of the more important remedies—of their value and method of use—can be made. For details the reader is referred to special treatises on bacteriology.

It is now known that many and probably all pathogenic germs produce in the animal organism two classes of substances capable of violently affecting nutrition, which substances are believed by chemists to be of albuminous nature.

To one class has been given the name *toxin*, to the other that of *antitoxin*. The toxin is the substance produced by the bacteria beneficial to the bacteria themselves, whilst the antitoxin, although produced by the bacteria, is hostile to them. In infectious diseases there is a battle between the toxins and the human animal aided by the antitoxins. The toxin has a twofold action. It acts locally as a poison and also affects the general system. Thus, the bacillus of diphtheria, growing upon the throat, forms there a toxin which attacks the immediately surrounding tissue, and so weakens it that the germ is capable of overcoming the natural resistance of the part. By and by, as the toxin is absorbed into the blood, it affects the general system and produces the constitutional symptoms and some of the wide-spread lesions of diphtheria. That the *rôle* of the toxin is important is shown by the fact that various pathogenic bacteria introduced into the living animal without any accompanying toxin are unable to overcome the resistance of the tissues and fail to develop. The antitoxin is in some way destructive to the bacteria; how it acts is still a matter of theory; it is proved that it is not a germicide and is not capable of killing the pathogenic organism. By some it is thought to act chemically upon the toxin, but the present evidence renders this improbable. The most plausible explanation is that the antitoxin in some way so affects the protoplasm that the latter is able to resist the action of the toxin. If antitoxin be given to an animal suffering from infectious

disease due to the local lodgement of a pathogenic germ, the first evidence of its beneficial action is the failure of the germs to grow, though they are not killed.

Some years ago the whole world was excited by the alleged discovery by Koch of a method of curing *phthisis*. The *tuberculin* of Koch was simply an impure toxin. When the tubercle bacillus grows in the human lung, the toxin which it forms slowly kills the tissues and produces ulceration; whilst doing this, it also finds its way into the blood and causes the so-called hectic fever and the other constitutional symptoms of chronic tuberculosis. When Koch's tuberculin—that is, tubercular toxin—is injected into the blood in a certain small quantity, it produces no febrile reaction in the normal individual because there is not enough of it present in the system. If, however, the injected toxin be added to a toxin which has been previously produced in the body, and which is already in the blood, the aggregate amount will be capable of producing a hectic fever, which will demonstrate the existence of a toxin-producing focus in the body,—*i.e.*, of tuberculosis. At the same time the injected toxin will reinforce the local action of the bacillary toxin, and so bring about rapid ulceration of the lung and discharge of the tubercle. The very setting free, however, of the tubercle bacilli favors their entrance into the lymphatics and the blood-vessels, and consequent dissemination throughout the body, so that a general tuberculosis has often immediately followed upon the treatment of a local tuberculosis by injection of tuberculin. The use of tuberculin has, therefore, justly passed out of vogue as a therapeutic agent. It is largely used, however, as a diagnostic measure by the veterinarian. Indeed, it has been employed for this purpose in human medicine, but the danger of hastening the tuberculous process is so great as to render its use unjustifiable.

The only toxin used to-day as a curative agent is that produced by the *streptococci*. Several cases of carcinoma have been noted in which, abscesses forming in cancerous growths, the tumor disappeared. This led to a trial of the streptococcus toxin as a curative agent in various *malignant growths*. The results, however, have not been very encouraging, and we have seen the added burden of septicæmia prove disastrous to a system already exhausted by cancer.

Diphtheria.—Without discussing the statistics of the subject, it seems sufficient to say that the value of antitoxin in diphtheria appears no more doubtful than is that of quinine in malaria. It is, however, essential that the antitoxin be used early, as it acts chiefly by arresting the growth of the bacillus. If the antitoxin be given late in the disorder it may arrest the further growth of the germ, but the patient may die nevertheless, because the tissues are already fatally poisoned with the toxin, or, perchance, have already undergone an irreparable degeneration. Again, there is in every bad case of diphtheria after the first twenty-four hours a general septic infection: so soon as lodgement has been fairly effected by Löffler's bacillus, and local tissue-change set in, streptococci and other septic germs

begin to develop rapidly in the dying tissues, and very soon give origin to a general septic infection, which in most fatal cases of diphtheria is an important factor in the causation of death. Evidently a Löffler's bacillus antitoxin is useless against a streptococcus toxin.

The absolute importance of the early use of the antitoxin during diphtheria is very evident. There are very few, if any, well-observed cases of diphtheria on record in which it has been positively determined that the antitoxin, administered during the first few hours after the outbreak of the disease, has failed to bring about a cure. On the other hand, statistics seem to show that if the injection be postponed to the fifth day, the mortality-rate is not reduced by the use of antitoxin. Our modern municipal scientific methods, notwithstanding all their laudations, are liable to become causes of death. A case of suspected diphtheria presents itself to the practitioner ; already the child has been sick, it may be, one or two days. A culture-tube is prepared, sent to the municipal laboratory, examined, and the result sent back to the practitioner, who then goes to see the patient. It is very fortunate if not more than one day is lost in this way, and the loss of those hours may well mean the loss of the life, for the time has elapsed during which the antitoxin would best act. There is no reason at present for believing that the antitoxin used in moderate quantity does harm when the child has not diphtheria. When, therefore, any case presents the clinical aspect of diphtheria the antitoxin should be used at once. For educational purposes, and for rendering definite our knowledge, the municipal laboratories are very useful; for purposes of treatment the less attention paid to them probably the better for the patients.

The use of antitoxin in any case of diphtheria should not interfere with the usual local and general treatment.

As it is never possible in any case of human diphtheria to know how much of the toxin is in the system, exact antitoxin dosage is impossible, but some general working rule must be formed, especially as there are a large number of serums upon the market of varying strength. Universal consent now seems to have been given to the recognition of Behring's antitoxin unit, which is one cubic centimetre of an antitoxin serum of such strength that this amount of it is capable of overcoming ten times the minimum fatal dose of the toxin for the guinea-pig. The antitoxin solution should be injected deeply into the buttocks or back with every possible antiseptic precaution.

Two methods of use of the antitoxin are in vogue. In the one which is especially advocated by J. H. Musser, small doses are given at short intervals. For children up to two years, who are seen early in the disease,—that is, on the first or second day,—and for mild cases 600 units are sufficient. If stenotic symptoms are present a dose of 1000 units should be given. In older children with a mild attack of the disease the initial dose should be 1000 units. In cases of longer duration with marked glandular swelling a double dose is needed ; both of these doses are to

be repeated if needed within twenty-four hours. For older children with very severe symptoms 3000 units should be given. The second dose in all cases should be 600 to 1000 units.

The second method consists in the administration of large doses at longer intervals. The doses recommended by the American Pediatrical Society are as follows: for children over two years in all severe cases, and in laryngeal cases, the initial dose is to be 1500 to 2000 units, to be repeated in eighteen to twenty-four hours, with a third dose, if needed; for children under two years and mild cases over two years the initial dose is 1000 units.

On the continent of Europe even larger doses than these are employed; the amounts recommended by some English authorities are so extraordinary as to throw great doubt upon the activity of English serum. Thus, according to the conclusions of the London Clinical Society, to the adult no initial dose under 6000 units is likely to be effectual, whilst the amount given in each case almost always reaches 20,000, and not seldom 50,000 units.

It is affirmed that the milder method is less apt to be followed by disagreeable antitoxin symptoms; but as these disagreeable symptoms are of little importance, the superior promptness and certainty and the avoidance of frequent disturbance of the patient which attend the more heroic method seem to us to make it preferable.

In most cases the injection of the antitoxin is followed in a very few hours by a fall of temperature and a decrease of the local diphtheritic symptoms. Occasionally, but not usually, this amelioration is preceded by a temporary rise of temperature. Sometimes the disagreeable symptoms produced by the injection appear in a few hours; perhaps more commonly they are not developed until six to nine days; and it is affirmed that they may be delayed to nine weeks, and have led to the mistaken diagnosis of scarlet fever or other exanthema. The characteristic symptoms are rise of temperature, with eruption upon the skin, and in several cases swelling and pain in the joints. The skin eruption may be purely erythematous, is often scarlatinoid, and perhaps as frequently rubeoloid, and sometimes takes the form of a severe urticaria. There is evidence to show that these after-effects follow much more frequently upon the use of diluted antitoxin than after injections of concentrated serums, and it seems to us probable that they are produced in some way by the serum itself and not by the antitoxin.

Tetanus.—The results of the antitoxin treatment of tetanus, while not nearly so striking as those of diphtheria, seem to warrant further trials of the method. In more than one hundred cases we have found recorded the mortality has been in the neighborhood of thirty per cent., but the results are so complicated by various circumstances that it is impossible to draw any positive conclusions from so few cases.

In the laboratory tetanus can be cured with almost absolute certainty by its appropriate antitoxin, but under these circumstances it is known

definitely how much tetanus toxin has been given to the animal, and the antitoxin is administered just before or immediately with the toxin; whereas in human tetanus the man is usually saturated with the toxin of the disease for hours or days before the antitoxin can be given. Very rarely in these human cases is the inoculation directly with the toxin, but with the bacillus, which takes usually from three to eight days before it is sufficiently developed to produce enough toxin to cause an outbreak of symptoms, so that there may be complete general saturation of the system when the apparent disease first appears.

Unfortunately, the unit of dose for the tetanus antitoxin does not seem fully established. Behring* has prepared a toxin of such power that one cubic centimetre will kill in from four to five days four million grammes of living tissue. Behring's unit for tetanus antitoxin is the amount sufficient to neutralize ten cubic centimetres of this test-toxin. The dose, according to Behring, should be at least one hundred units (ten cubic centimetres of Behring's serum). Tizzoni has objected to Behring's conclusions very strenuously.

Erysipelas.—It is probable that there are various poisonous streptococci, but clinical experience seems to show that the streptococcus antitoxins now in the market are active in all forms of streptococcus diseases; at least, there are as yet no means of distinguishing between the different forms of streptococci poisoning. In erysipelas and allied septicæmia the remedy may be tried with fair hope of success. In a discussion before the Philadelphia Gynæcological Society, the result arrived at was that when the injections of serum were begun early in pure streptococci cases they were of value, but that in cases of puerperal septicæmia they were often of little effect, because the sepsis was not due to streptococci. In advanced *diphtheria*, in *scarlet fever*, and in various cases with secondary streptococcus infection the antitoxin may be of service. There is no generally recognized unit of streptococcus antitoxin, and therefore cannot be any definite dosage; so that the practitioner can only follow the directions given with the antitoxin serum by the manufacturing firm.

Cholera.—Lazarus discovered that the blood-serum of human beings who have recovered from an attack of Asiatic cholera possesses properties which render it capable of protecting animals from fatal doses of the spirillum of Asiatic cholera. He regarded this substance as being of the nature of an antitoxin, and the protective action of the human serum as similar to the antitoxin of diphtheria, tetanus, etc. The studies of R. Pfeiffer, however, have shown that the principle contained within the blood-serum is not of the nature of an antitoxin, but is bactericidal; it acts by causing rapid disintegration of the introduced cholera organism, and thus prevents the rapid multiplication that brings about the death of the exposed animal. A few minutes after the simultaneous introduction of the cholera vibrio and of the blood-serum into the peritoneal cavity of small animals,

* *Deutsche Med. Wochenschrift*, 1900, xxvi. 29.

such as the guinea-pig, the micro-organisms begin to disintegrate, and very soon they are completely destroyed.

Pfeiffer also showed that dead cholera organisms are still toxic and capable of acting similarly to the living germs. Haffkin has applied this method to the immunization of human beings to cholera; he cultivates the germ in bouillon, and after a certain growth has been obtained, heats sufficiently to kill the germ without completely destroying the cholera poison which adheres to its body, and which is a very sensitive substance. Injections of such cultures in human beings are followed by a local reaction and febrile movements and the appearance of a protective substance in the blood-serum in man similar to that present after an attack of the disease. Two injections are commonly made at the interval of about a week, after which the protection of the individual is believed to be complete. This method has been applied on a large scale in India, and apparently with a measure of success.

Bubonic Plague.—Pest.—The discovery by Yersin in 1894 of the bacillus of the bubonic plague has introduced protective measures to be employed in combating that disease. Several methods are now in use; that of Yersin consists in the immunization of horses or other large animals to injections of the plague bacillus, and the use of the blood-serum obtained from these animals in a manner similar to the employment of the antitoxin of diphtheria.

Haffkin's method, which has been used on a larger scale, and apparently with less doubtful results than that of Yersin, is in principle similar to the protective inoculation for cholera. Bouillon cultures of the plague bacillus (the organisms being obtained directly from human cases of the plague) are incubated for about two weeks. The bouillon is finally heated to 60° C., for about twenty minutes, in order to kill the bacillus, after which half of one per cent. of carbolic acid is added in order to preserve the serum from accidental contamination by other micro-organisms.

The injections are made into the soft tissues of the thigh, the entire culture being used. Two injections are usually employed, at intervals of six days. The symptoms are elevation of temperature and swelling about the point of inoculation, most marked after the first injection. The second inoculation is believed to give protection. The statistics gathered from India, where the plague has prevailed, are highly encouraging as to the value of this procedure. The serum is of no use in the treatment of developed cases of the plague.

Another method of protection which is being employed is that of Lustig, who produces from the dead plague bacillus, by treatment with acids and then alkalies, an active nucleo-proteid, whose inoculation into animals and human beings gives active immunity to the plague organism. The blood-serum from animals so immunized may be used in the treatment of the developed plague, or, injected into healthy human beings, affords a passive immunity which, however, endures only a few weeks.

It is, therefore, capable of use in protecting for a short time a community exposed to the plague, although less reliable than Haffkin's serum. Its advantage is that it affords immediate protection, whereas the other means employed require a number of doses before the protective action appears.

The blood-serum of human beings and animals who have withstood injections of the plague bacillus possesses agglutinating properties of the plague organisms ; this agglutination, however, does not appear early in the infection, but is a phenomenon of the convalescence. Its usefulness, therefore, in the diagnosis of the plague is somewhat doubtful.

Snake-Poisoning.—Sewall appears to have been the first to demonstrate the possibility of producing immunization against the venom of serpents, having proved as long ago as 1887 that it was possible by a series of inoculations of increasing intensity temporarily to immunize pigeons against the rattlesnake-poison. As the result of experiments by various observers, it has been established that venomous serpents are poisoned by snake-venom only with the greatest difficulty ; that the ordinary non-poisonous snakes share this immunity to a distinctly less degree ; and that certain of the higher animals, notably the mongoose, are distinctly resistant to the poison. It is probable that the immunity in the higher animals is an inherited, "acquired character," due to the repeated survival of generations of bitten mongoose, the immunity of the individual being partially transmitted to the offspring.

The serum of the blood of the artificially immunized animal has been found to be of remedial value in snake-poisoning, and has been put upon the market commercially. Its use for the production of immunity is justifiable only in certain conditions when there is about to be an extraordinary exposure to the possible snake-bite, since the immunity it confers lasts only for a short time. The value of the serum as a curative agent has, however, been proved not only in the laboratory, but also in a number of recorded cases of snake-bite ; so that it should be carried by those whose duties or desires lead them into tropical countries where poisonous serpents abound.

It has been long known that the venom of a poisonous serpent may be taken by the mouth with impunity, and it has been found that when so exhibited the venom is antidotal to itself injected into the subcellular tissue or into a vein. It has been further demonstrated that the venom may, by forced filtration through porcelain, be divided into two parts, one of these parts containing the toxic portion of the venom, the other an antidote to the toxic principle. The toxic principle undergoes digestion in the stomach, the antidote passes through the stomach into the blood. Hence the explanation of the curious antidotal value of the poison against itself.

According to the reports of missionaries, the various compounds prepared by the witches in Africa for the cure of snake-bite have the liver of the serpent in their combination ; and T. R. Fraser, of Edin-

burgh, has experimentally proved that the bile of poisonous serpents is a very active antidote to the poison, neutralizing the venom when mixed with it in equal quantities. Even the bile of ordinary mammals has a feeble antidotal power. When after a bite it is possible to kill the snake, all of its bile should be injected into the immediate neighborhood of the wound.

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5. MAIRET and BOSC . A. de P., 1896, 100.

SPLEEN.

1. CLARK . . . . . Ed. M. J., 1898, iii. 152.

THYMUS GLAND.

1. MACKENZIE . . . A. J. M. S., 1897, cxiii.
2. FISCHER . . . . . D. M. W., 1898, xxiv.; Therap. Beil., 49.

FAMILY IV.—ANTIPERIODICS.

CINCHONA. U. S.

THE U. S. Pharmacopœia formerly recognized three varieties of Cinchona,—namely, *Cinchona Flava* or *Yellow Cinchona*, *Cinchona Pallida* or *Pale Cinchona*, and *Cinchona Rubra* or *Red Cinchona*. At present, under the general heading of Cinchona, it recognizes the bark of all species of the genus yielding when assayed by the official process not less than five per cent. of the alkaloids and two and five-tenths per cent. of quinine.

The genus Cinchona contains numerous species, yielding quinine and its congeneric alkaloids, indigenous to the western and northern portions of South America, where they grow upon the slopes of the Andes, at an altitude of from five to ten thousand feet. Formerly the only cinchona known to commerce was collected by the *cascarilleros*, or woodmen, and exported in large bundles or bales, usually covered by raw hide (*seroons*). The natural commerce, however, in the quinine barks has almost disappeared under the conjoint influence of excessive production by cultivation and reckless destruction of the original forests. At present the world's market is supplied with the cinchona barks chiefly from plantations in the Himalaya Mountains, in Ceylon, and in Java. For a full account of this most important industry the reader is referred to the very able article by H. H. Rusby in the United States Dispensatory.

CHEMICAL CONSTITUTION.—Besides tannic, kinic, and kinovic acids, and other important substances, the cinchona barks contain quinine and quinidine, cinchonine and cinchonidine. Out of these alkaloids quinicine and cinchonicine are readily formed artificially, but, so far as is known, they do not exist in nature. There are therefore two isomeric alkaloidal groups : quinine, quinidine, quinicine ; cinchonine, cinchonidine, cinchonicine.*

QUININA—QUININE. U. S.

This alkaloid was first distinctly separated from the other ingredients of the bark by Pelletier and Caventou in 1820. When quinine is precipitated by an alkali from a solution of its salt, it usually falls as a

* Out of the quinine alkaloidal groups have been formed by chemists various isomeric alkaloids. For physiological study of these, see *Archiv. Physiol. Norm. et Path.*, 1893, v.

hydrate, which may be crystalline. By sufficient heat the hydrate is melted and the water is driven off. On cooling, the alkaloid, now free from water, forms a white, opaque, crystalline mass.

The neutral, official *quinine sulphate* (QUININÆ SULPHAS, U. S.) occurs in light silky crystals, soluble in seven hundred and forty parts of cold or in thirty of boiling water, readily soluble in alcohol, very freely so in acidulated solutions, nearly insoluble in ether. Therefore, when it is administered either by the subcellular tissue or by the rectum the alkaloid should be given in the form of the bisulphate and in distinctly acidulated water.

The authority mentioned found that one thousand parts of blood which was defibrinated and deprived of its gases at a temperature of 36° C. dissolved in an hour only 0.398 part of pure quinine. Water saturated with carbonic acid gas dissolves the quinine sulphate pretty freely; and Kerner also experimentally determined that when a neutral solution of a salt of quinine is added to a very dilute solution of sodium carbonate no precipitate occurs. It would appear, then, that the quinine is held in solution in the blood by reason of the loosely combined carbonic acid gas in that fluid.

PHYSIOLOGICAL ACTION.—*Local Action.*—Quinine is distinctly irritant to the mucous membranes, but has little or no influence upon the sound skin. As stated as long ago as 1765 by Pringle, the cinchona bark itself is distinctly antiseptic.* More recent researches have demonstrated that quinine is actively germicidal, and that in the proportion of one part to three hundred it will preserve for a long time flesh, meal, milk, butter, urine, albumin, etc., and will check very markedly the alcoholic fermentation in honey or in syrup.

According to the experiments of Binz, the larger infusoria, such as Paramecia and Colpoda, are killed by a solution of quinine of the strength of 1 in 800 immediately, of 1 in 1000 after some minutes, of 1 in 20,000 after some hours. Upon the ordinary mould Penicillium, upon Vibrios and Bacteria, as well as upon the higher infusoria, quinine acts with a similar fatality. In the case of the Vibrios and Bacteria a decidedly stronger solution than the one mentioned is required to quiet movement. Bochefontaine found that a solution of one per cent. was needed for a vigorous rapid action, and that some active granules could even be found in it after three days.

The fact that fungi will appear after a time in an ordinary solution of quinine sulphate demonstrates that at least upon some of the lower organisms it has some, but comparatively little, influence, although on others it acts with much power.

Absorption and Elimination.—Owing to its insolubility in simple water or alkaline solutions, quinine can enter the body with rapidity only under circumstances in which it is exposed to the solvent power of acids.

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* Mayer, Pavisi, Hallier (*Das Cholera-Contagium*, Leipsic, 1867), Herbst, Polli, and especially Binz (*Virchow's Archiv*, 1869, xlvi. 68; and *Untersuchungen über das Wesen der Chininwirkung*, 20).

Taken into the stomach, the quinine salt is dissolved by the acid gastric juice; but if not absorbed at once, passing into the intestines, it is liable to be precipitated by the alkaline juices, and especially by the bile acids, which form with it insoluble salts; that under these circumstances a considerable portion of the quinine escapes absorption is shown by the fact that Kerner[1] and others have found it in considerable quantity in the fæces.

Quinine is eliminated chiefly through the kidneys,* escaping in large part unchanged, but probably in part undergoes alteration.†

According to Briquet,[2] quinine may generally be found in the urine half an hour after the administration of a large dose. Its removal, according to the researches of Binz, goes on slowly, for it is stated that in six experiments only a little more than two-thirds of the ingested quantity was excreted in the first forty-eight hours. Further, De Renzi,[3] Yvon, and Dietl[4] have found it in the urine six or seven days after the ingestion of the last dose. It is probable that some of the quinine is eliminated through other channels than the kidneys, since Binz has found it in the saliva of a poisoned dog, and Landerer[5] states that he has detected it in the urine, sweat, tears, milk of nursing women, and in the serum of dropsical effusions, while Albertoni and De Renzi find it abundant in the bile when it has been taken by the mouth, but not when it has been given hypodermically.

As the blood is alkaline, *a priori* it would be expected that the quinine salt would be precipitated in the blood; that this does not occur is, according to the researches of Kerner, due to the solvent power of the carbonic acid in normal blood.

The question as to the rate and completeness of the elimination of quinine is one of great practical importance. It is evident that it is both absorbed and eliminated more rapidly when it is given in solution or in the form of the acid salt than when taken in pill or capsule. Under favorable circumstances, with the dose not too large, it is probable that absorption is practically complete within two hours after the taking of the quinine into the stomach, so that the maximum effect of the single dose is probably reached in from one to two hours. Thau determined that from a third to somewhat less than half of the ingested quinine

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* See analyses of Landerer (*Repertorium für Pharmacie*, 1836, xxv.), of Dietl (*Wiener Medizinische Wochenschrift*, 1852), of Briquet, of Binz, and of De Renzi (*Bull. Thérap.*, xci. 45).

† G. Kerner (*Pflüger's Archiv für Physiologie*, 1870) asserts that the quinine as excreted is in an amorphous, uncrystallizable form. He also has discovered in the urine of persons taking quinine a peculiar substance, sometimes amorphous, sometimes in acicular prismatic crystals, free from bitter taste, possessing the quinine inflorescence, which he believes to be a derivative formed in the body from the ingested alkaloid. He has not been able to get this substance in such quantity as to analyze it or further examine it, but has produced a principle (*dihydroxyl-quinine*) which he believes to be identical with it by acting on quinine with the potassium permanganate. An elaborate series of experiments have shown that the dihydroxyl-quinine is physiologically inert. This dihydroxyl-quinine must be produced in small amount, if at all, as there is abundant evidence that quinine is largely excreted as quinine (see *Pharm. Journ. and Trans.*, ix. 125).

escapes from the body in the first six hours, and that in the first twelve hours about three-fourths are excreted. Welitschkowski[6] found an elimination of sixty-five per cent. the first day and twenty-five per cent. the second day. Prior gives the second day as the usual final limit of elimination. We think it more than probable that after *a few doses the alkaloid is practically eliminated in forty-eight hours*, but that when it has been given continuously, or when kidney disease or great feebleness of circulation exists, the system may contain a notable amount of the quinine for a longer period. The researches of Welitschkowski are in accord with those of Jürgensen and Thau in showing that in cardiac and renal disease and in low fevers elimination proceeds very slowly, more of the alkaloid being thrown off in the second than in the first six hours after its ingestion.

General Effects.—The first symptoms of cinchonism, as produced by full therapeutic doses (ten grains) in man, are usually ringing in the ears, slight fulness in the head, and perhaps some deafness. With the use of larger doses these symptoms are intensified : the deafness is very marked, disturbed vision * may exist, and the flushed face, with a sense of distention in the head, may point towards a cerebral congestion, which is in some cases relieved by spontaneous epistaxis. In decided cinchonism, giddiness and staggering in walking are very common. After toxic doses, severe headache, delirium, stupor, complete deafness and blindness, dilated pupils, embarrassment of respiration, great weakness, convulsions, paralysis, and finally collapse may result, either comatose or delirious. Quinine deafness usually passes off rapidly, but may be permanent.

In the lower animals large doses of quinine frequently cause violent epileptiform convulsions. Given to dogs in sufficient quantity, it produces restlessness, followed by muscular tremblings, which have been compared to those of paralysis agitans, loss of power deepening into more or less complete paralysis, great dyspnœa, and cerebral symptoms, such as anæsthesia, blindness, stupor, or violent delirium, dilated pupils, coma, and convulsions. When the drug is introduced by the stomach, vomiting generally occurs, and at times diarrhœa also.† Death has been shown by Heubach to be produced, at least in the lower animals, by a failure of the respiration.‡

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* We have seen complete temporary amaurosis produced in a lady by twelve grains of quinine.

† See F. M. Melier (*Mémoires de l'Académie*, 1843, xii. 722), William O. Baldwin (*Amer. Journ. Med. Sci.*, April, 1847), and P. Briquet (*Traité thérap. de Quinquina*, Paris, 1855).

‡ The present is perhaps as suitable a place as any to notice certain researches upon the relations of alkaloids to protoplasm. The relation between medicinal substances and the tissues upon which they act is certainly a very close one, and very probably is chemical in its nature. Rossbach (*Pharm. Untersuch.*, i. iii.) found that various alkaloids sensibly modify the properties of albumin, and believes that they form a chemical compound with it. Under the influence of the poison the albumin coagulates at a much lower temperature, and is deprived of its affinity for ozone. The alkaloids also precipitate the albumin from its ozonized solution.

A close physiological study of quinine can best be made by investigating its effects upon the different systems of organs *seriatim*, and this shall now be done.

Cerebrum.—According to the experiments of Briquet, a solution of quinine sulphate injected into the carotid will in some cases produce meningitis. In doing this, it is evident that the salt acts as an irritant to the membranes of the brain rather than as a nervous stimulant: indeed, experimental evidence proving that quinine is a cerebral stimulant seems to us to be wanting. The chief proof that the alkaloid does act as a nervous stimulant lies in the fact that persons who have been taking it regularly for some time will occasionally, upon the sudden withdrawal of their daily dose, manifestly be less active without than with it. Briquet may be right in his belief that in small doses it acts as a nervous stimulant, but the proof of his correctness at present is clinical rather than experimental. When given in toxic doses to the lower animals, probably all of the cinchona alkaloids produce epileptiform attacks.

J. Jakoubowich[7] has noticed such effect with quinine in dogs, and it has been produced with cinchonidine in various animals. Chirone and Curci found that in the pigeon this action of cinchonidine is prevented by ablation of the cerebral hemispheres, but Albertoni[8] objects with much force that these observers gave the pigeon the alkaloid too soon after the ablation, while it was still profoundly affected by the shock and hemorrhage of the operation. Albertoni found that, if the pigeon is allowed to recover, the cinchonidine is capable of causing convulsions; also that in dogs with the motor zone of the cerebral cortex destroyed, the alkaloid causes epileptiform attacks, and that therapeutic doses do not increase the excitability of the cerebral cortex in the dog.

The production of convulsions in the lower animals is of great interest in connection with the fact noted for quinine by Brown-Séquard and confirmed by Albertoni as regards cinchonidine, that in epileptics the attacks are rendered decidedly more frequent by the cinchona alkaloids. The present evidence indicates that this increase is not due to an influence upon the cerebral cortex, but can hardly be considered sufficient to be conclusive. In very large doses quinine without doubt abolishes the functions of the cerebrum.

Louis Dupuis[9] found that reflex action may be normal in poisoned dogs and rabbits, although there is complete loss of sensibility: if this be correct, the toxic dose of quinine must paralyze the perceptive centres in the cerebrum.

Special Sense.—The disorders of special sense produced by quinine seem to be the result of a direct action upon the peripheral sense organs. The deafness and *tinnitus aurium* are due to congestion in the labyrinth of the internal ear.

Kirchner[10] found, in rabbits, cats, and guinea-pigs which had been poisoned with quinine or with salicylic acid, very great congestion of the internal ear and of the labyrinth, with bloody exudation, and, in some cases, the ear-drum swollen

into a bladder-like body by serous exudation. Roosa[11] affirms that in man sufficient doses of the alkaloid cause congestion of the blood-vessels of the middle ear, and H. C. Wood has seen. in a person who suffered from chronic inflammation of the middle ear of one side, a small dose of quinine produce tinnitus aurium of the diseased ear, without affecting the sound ear.

More or less complete amblyopia may be produced by quinine and end in permanent loss of sight.* In most of the numerous recorded cases the amount of quinine ingested has been very large, but we have seen in one individual twelve grains of quinine repeatedly produce temporary blindness. The disturbance of vision may come on abruptly or gradually. When fully developed it is usually accompanied by dilatation of the pupils, absence of the light-reflex, and imperfect response to accommodative effort. There have also been noted nystagmus, divergent strabismus, anæsthesia of the conjunctiva, and increased ocular tension.

When the blindness is not complete there is commonly pronounced contraction of the field, or in rare cases scotomata. The disturbance of vision may subside with the specific action of the drug, but it may persist for days or months, or even permanently. The color-sense is probably first affected; certainly it usually does not recover itself until after the return of central vision. The ophthalmoscopic examination commonly, but not always, has revealed pallor of the optic disks, with excessive lessening in the size of the retinal vessels; indeed, in some cases there has been complete obliteration of the vessels of the optic nerve. Graefe has, however, noted quinine blindness with normal ophthalmoscopic appearances, whilst Dickinson describes congestion of the retina and choroid, and Gruening[91] and Mellinger[92] record hyperæmia of the disk. The pathogenesis of quinine amaurosis in dogs has been studied by Brunner, de Schweinitz,[93] Barabaschew,[94] de Bono,[95] Holden,[96] and Druault.[97] The visual disturbances are due to a degeneration of the ganglion cells of the retina and the optic nerves, which, with the tracts, finally become completely atrophic. The primary lesion is in the nuclei of the cells, where it may be demonstrated ten hours after the injection of the drug.

The breaking down of the least resisting elements of the inner retinal layers—the ganglion cells and nerve-fibres—is caused partly by a lessened blood supply due to spasm of the retinal vessels and partly by a direct action of the drug on the protoplasm of the cells. An ascending atrophy of the optic nerve follows. The spasm of the retinal vessels has been attributed to an action of the drug on the vaso-motor centres, which is unlikely, and to its influence on the vessel walls or on the perivascular vaso-motor plexus. De Bono's theory, that paralysis of the neuro-epithelium of the retina causes the amaurosis, has not been confirmed.†

* According to Rogers (*Journ. Amer. Med. Assoc.*, 1889), one or two hours after the ingestion of twenty grains of cinchonine sulphate there can usually be observed paresis of accommodation, which may increase until it becomes almost complete. It seems hardly possible that this phenomenon, if an habitual one, could have been overlooked by other observers.

† For discussion of the subject, with *résumé* of the literature, see *Toxic Amblyopias*, George E. de Schweinitz, 1896, and Norris and Oliver's *Diseases of the Eye*, 1900, iv. 832; for case of blindness lasting twenty-one days, see *Brit. Med. Journ.*, 1886, i. 823.

Spinal Nerves and Centres.—Schlockow was the first to notice a stage of increased reflex activity produced in the frog by quinine; its existence was subsequently denied by A. Eulenburg,[12] but has been reaffirmed by H. Heubach[13] and by David Cerna,[14] who agree in finding that it occurs only after very minute doses. In his investigations made in the laboratory of the University of Pennsylvania, Cerna found that this stage of excitement is probably caused by a stimulant influence upon the peripheral sensory nerves, as it did not occur when the abdominal aorta was tied previous to the exhibition of the alkaloid. Two facts, first pointed out by T. A. Chaperon,[15] have been so abundantly substantiated that we must accept them as established. They are, that in *small* doses quinine causes in the frog a lessening of the reflex activity, which is removed by section of the medulla, and in *large* doses it produces a permanent palsy of reflex activity. The only explanation of the first lessening of reflex activity which is at present plausible is that it is due to stimulation of Setschenow's centre.

Sedgwick[16] combats the theory just spoken of; he believes that the inhibition of the reflexes is such as occurs when a sensitive nerve is galvanized, and is the result of a stimulation of the peripheral afferent cardiac pneumogastric nerve-endings by the quinine. He bases his theory chiefly on the fact which he has discovered, that atropine prevents the primary inhibition of reflexes by quinine. This is, however, readily explainable without the adoption of the theory of Sedgwick, and the results which he obtained after division of the pneumogastrics are scarcely in accord with his theory.

The cause of the permanent influence upon reflex activity has not yet been accurately determined, but there is reason for supposing that peripheral sensory nerve-endings are first paralyzed.

Chaperon and Wild found that the motor nerve-trunks are unaffected, but this does not prove that the spinal centres are paralyzed, especially as Wild's experiments seem to show that the nerve-endings in the muscles are attacked. (See below.) A. Eulenburg asserts that voluntary movements persist after reflex actions, and that the quininized frog will turn into its normal position when laid upon its back, although ordinary reflex actions are completely abolished. This, if correct, certainly shows that it is either the sensory nerves or the receptive centres of the cord whose paralysis by quinine puts an end to ordinary reflex movements. So that, accepting the various results reached by experimenters, it is probable that in frogs quinine first excites and then paralyzes the peripheral sensitive nervous system.

Muscles.—According to the experiments of H. Kobert,[17] very large doses of cinchonine, and probably therefore of quinine, lessen the excitability of the muscles. This is confirmed by the experiments of R. B. Wild,[18] who finds that solution of quinine 1 to 1000 brought in contact with the isolated muscles of the frog diminishes the irritability of the muscle and alters to some extent its relations with stimulation. The peripheral nerve-endings appear to be more sensitive than is the muscle, for when a solution of 1 to 4000 was employed, galvanization of the

a sensitive nerve nor asphyxia was able to produce vascular contraction and rise of blood-pressure, and Jerusalimsky[22] asserts that in frogs dilatation of the vessels can be seen.* Further, Kobert, experimenting with the excised organs of the warm-blooded animals, and Wild, experimenting with the tortoise, prepared according to the method of Stevens and Donaldson, have found that very weak solutions of quinine sulphate (1 part to 5000) cause enormous dilatation of the vessels, with consequent increased rapidity of passage through them of liquid under pressure. It is probable, therefore, that the *fall of the arterial pressure in poisoning by quinine is in part the result of an action upon the vessels.*†

Both Schroff and Jerusalimsky noticed that the fall of arterial pressure produced by quinine is preceded by a rise of the pressure, accompanied by an increase of the cardiac action. This observation has been confirmed by G. Sée and Bochefontaine ;[23] but no observer seems to have shown that the rise of pressure is more than a temporary phenomenon. Sée and Bochefontaine affirm that the increased cardiac action continues some time after the pressure begins to fall. The primary rise of pressure may be the result of a stimulant action upon the vaso-motor centres, as Jerusalimsky found that it was not produced after division of the cord. It is not improbable that it is due to disturbances of respiration. Jerusalimsky attributes the increase in the pulse-rate to paralysis of the inhibitory apparatus,—a view which is supported by the assertion of Cerna that previous section of the pneumogastric prevents the quickening of the pulse-rate.

We have never been able to perceive any depressant action upon the circulation in man after ordinary therapeutic doses (three to five grains) of quinine, and we believe that in tonic doses quinine produces no perceptible sedation of the circulation, but that the largest antiperiodic doses have a distinct influence.‡

Blood.—According to Bonorn and Arvedi, to Magendie, to Monneret, to Melier, and to Baldwin, in animals killed with quinine the blood is found to be dark, defibrinated, fluid, and incapable of forming a clot. Briquet, however, denies that this alteration of the blood is constant, or even common, in quinine-poisoning, as he found it in only four out of twenty-three dogs so sacrificed ; and he believes that it is merely an accident dependent upon the method of death,—a conclusion which has

* M. Chirone believes that by quinine the heart is arrested in *active* dilatation. The theory is very improbable. See *Rivista Clinica di Bologna*, abstracted in *Journ. de Physiol. Norm. et Patholog.*, 1876, 844.

Heubach, in a series of experiments on the influence of galvanization of a sensitive nerve upon the circulation after the exhibition of quinine, failed to detect any paralyzant action of the drug, although in some of his experiments the reflex activity was paralyzed.

† When, in Wild's experiments, the action of quinine was maintained for a length of time, the dilatation was finally followed by contraction, which contraction was in all probability the outcome of a post-mortem rigidity.

‡ Some studies have been made upon the action of the drug on the capillaries of the brain, but the evidence is contradictory and insufficient. Consult *Psychological and Medico-Legal Journal*, 1875, 33 ; also *Archives of Medicine*, i. 33.

been confirmed by H. A. Hare. In a series of analyses Briquet found that the continued use of quinine augments the proportion of fibrin, but lowers that of the red corpuscles.

In 1867 * Binz announced the fact that quinine added to human blood in the proportion of 1 part to 4000 immediately checks and in a short time arrests the amœboid movements of the white blood-cells. Confirmation of this has been furnished by Scharrenbroich,[24] by Kerner,[25] by Geltowsky,[26] and by Jerusalimsky. The minimum effective strength of the solution has been found to vary in different species of animals, and even in different individuals of the same species.

It is a matter of great interest to determine whether quinine acts in the living organism as on the stage of the microscope; and, to settle this point, Binz[27] has experimented according to the method of Cohnheim. He found that when the mesentery of curarized frogs to which quinine had been given was exposed upon the stage of the microscope, no accumulation of white blood-cells in the small vessels, or passage of them out into the tissues, occurred upon irritation; or, if after a time these phenomena commenced, they were at once checked by a small hypodermic injection of the alkaloid. When the inflammatory process had already commenced in a "Cohnheim frog," an injection of quinine would cause the out-wandering of the corpuscles to cease, and would bring about a gradual clearing of the white cells from the choked-up vessels. Binz further took two young cats and, after poisoning one of them with quinine, examined their blood. In the blood of the unpoisoned animal the white cells were far more abundant than in that of the poisoned cat. From these facts Binz deduced the conclusion that quinine acts destructively in the system upon the white blood-corpuscles, in the same way as when they are out of the body. George R. Cutter[28] and H. A. Hare[29] have experimentally confirmed the effect of quinine in preventing the extrusion of white blood-cells from the frog's mesentery, and A. Martin[30] has also found that the action of the drug is apparent in the centre of parenchymatous organs, such as the liver. On the other hand, Schwalbe † could detect no difference in the blood of a cat before and after poisoning by quinine; and the experiments of Geltowsky upon frogs and guinea-pigs have yielded similar results: in all his animals after fatal poisoning by the alkaloid the movements of the corpuscles were found to be very active.

The correctness of the original observation of Binz, that quinine checks the out-wandering of the white blood-corpuscles in the irritated mesentery of the Cohnheim frog, must be considered as established, but it is not proved that the failure of the blood-corpuscles to escape from the irritated vessels is due to the arrest of their amœboid movements by the quinine.

In a series of experiments H. A. Hare found that the vessels in the cinchonized frog were much more contracted and had their walls much thicker than in a corresponding frog without quinine. This contraction of the vessels is thought by Hare to be the result of a direct action exerted by the drug upon the muscular coat of the arterioles. It is certain that the alkaloid reduces very markedly the force of the heart. It is, therefore, possible that the quinine prevents the out-wandering by les-

* *Archiv für Microscop. Anatomie*, 1867, iii. Consult also *Experimentelle Untersuchungen über das Wesen der Chininwirkung*, Berlin, 1868; *Virchow's Archiv*, 1869, xlv. 137; *Berlin. Klin. Wochenschrift*, Nov. 1871.

† Quoted by Kerner (*Pflüger's Archiv*, i. 203).

sening the force which is driving the corpuscles and at the same time increasing the resistance of the capillary walls.

It must be considered still doubtful how far quinine affects the white blood-corpuscles in the circulation even when it is administered in poisonous doses. Therapeutic doses certainly have no demonstrable effect.

It would seem that quinine acts also upon other portions of the blood than the white corpuscles.

Manassein[31] has found that in fever occurring in the lower animals the red corpuscles are diminished in size. If in this condition a decided dose of an antipyretic, such as quinine or alcohol, be given, and the temperature falls, the globules resume their normal size. That the change is due to the fall of the temperature rather than to a direct action of the drug is, we think, demonstrated by the fact of its occurrence whenever the fever-heat is lowered by the application of external cold. The experiments of Manassein, therefore, do not prove that quinine exerts any direct action on the red corpuscles.

The investigations of Binz[32] appear to show that the alkaloid lessens the ozonizing power of the blood; for he found that in young cats to which he had given a very large but not fatal dose of quinine the freshly drawn blood affected the tincture of guaiac much less than it normally should.

When blood is drawn from the body and allowed to stand, acid is developed in it. Zunst,[33] who has studied this subject most closely, divided the investigation into study of the production of acid in the time from the escape of the blood from the vein to its coagulation, and study of the slow changes which increase its acidity after coagulation until putrefaction has fairly set in. Binz believes that this development of acid is due to oxidation, and by an elaborate series of experiments has determined that quinine (also bebeerine sulphate and sodium picrate in almost as great degree) inhibits these changes very greatly in both their varieties. These experiments are in accord with the previous ones of A. Schulte:[34] the facts may, therefore, be considered proved.

If ozonized oil of turpentine be dropped into an alcoholic solution of guaiac resin, no alteration of color occurs; but if a drop of blood be added, the blue appears at once,—*i.e.*, the blood acts as a carrier of ozone from the turpentine to the resin. Binz has found that quinine, even in so small an amount as 1 part in 20,000, has a perceptible influence in preventing this. Similarly, when sodium carbonate is thrown into a dilute watery solution of indigo sulphate until the reaction is decidedly alkaline, and a little blood, and subsequently ten drops of ozonized turpentine, are added, a green color begins at once to develop, and in a little while passes into the clear yellow of isatin. In this case also the blood acts as a carrier of ozone; and Binz and his pupil Ransoné[35] have determined that quinine also inhibits this action, one part of it added to a thousand of the mixture delaying the change of color for an hour. In these experiments Binz used a large number of different salts

of quinine, and found that they acted identically. That the action of the alkaloid was on the blood, not on the indigo and guaiac solutions, was shown by the fact that when similar solutions without the blood were shaken in the air and absorbed ozone, the characteristic colorations of its action were produced just as readily when quinine was absent as when it was present. Binz also proved that the red corpuscles were the portions of the blood affected. On adding crystallized hæmoglobin from horses' blood to the guaiac solution he found that it acted as an ozone-bearer between the turpentine and the guaiac, and further demonstrated that quinine had the power of preventing this action.

As it is established that quinine exerts some antipyretic action (see page 539) in ordinary fever, it is a plausible theory that the lowering of temperature is due to a checking of the ozonizing power of the blood. To attribute, however, the general medical virtues of quinine to an action on the white corpuscles seems to us unreasonable ; for from the experiments of Binz himself upon the lower organisms it would appear that quinine acts upon all animal germinal matter ; and it is probable that the protoplasm of the nervous system, being more specialized than that of the white corpuscles, would be more susceptible to the influence of the alkaloid.

Binz states that both conine and camphor act more forcibly upon the white corpuscles out of the body than does quinine, and T. Lauder Brunton and Theo. Cash[36] have found that morphine, veratrine, and codeine check the ozonizing power of the blood, while digitalin, picrotoxin, and caffeine increase it. Each of these principles has its own peculiar physiological action, differing from that of quinine and the other alkaloids. It seems absurd to attribute such diverse physiological actions to the one common property of the group, and we think that we must consider the antozonizing power of quinine as simply one of its functions, and not as the basis of its relations with the human organism.

Uterus.—In 1871 Monteverdi[37] announced that quinine is an active uterine stimulant, but in so doing brought forward nothing that was novel.

As long ago as 1855 John S. Wilson[38] called attention to the uterine action of quinine, and in 1860 reasserted his belief, which in the mean while had been confirmed by J. H. Rich ; and in 1858 Jos. J. West[39] wrote, "Many regard the use of quinine as dangerous and even criminal in any disease in pregnant women. The belief of these persons is that this substance exercises a direct influence upon the uterus, *causing powerful contractions* and expulsion of the fœtus. And to support this notion they are ready to bring forward innumerable instances of abortion after its use,—of cases of sudden suppression relieved by a prompt use of the same remedy." He then goes on to say that these abortions, etc., were due to the intermittent fever, and not to the drug. Surely this is enough to show that the oxytocic action of quinine was believed in many years ago by our Southern practitioners.

The answer to the question, Has quinine ecbolic qualities? should be made out in three different ways. First, Is there any evidence of quinine producing abortion in healthy women or in females of the lower animals?

Second, How strong is the evidence of its producing abortion in women suffering from ague? Third, What is the evidence in regard to the action of quinine during labor?

In regard to the first of these sub-questions, the only affirmative evidence we have met with is in the experiments of Rancillia,[40] who saw abortion in two bitches follow the administration of from six to nine grains of quinine: as the pups in one case were already dead before the administration of the drug, it would seem that this investigation was not on such a scale as to be at all conclusive. Moreover, we have given quinine to two pregnant cats, in one case in sufficient quantity to cause death, without disturbing the products of conception. Furthermore, we have met with no evidence that quinine is capable of inducing abortion in healthy pregnant women. Sayre's[41] case is certainly no proof whatever that quinine will originate labor, as labor had commenced under the influence of the hot and cold douche and other measures employed *before* the quinine was given. Chiara,[42] of Milan, has furnished very strong evidence that quinine is incapable of originating uterine contractions in healthy pregnant women. In his public service, two doses of a gramme (15.34 grains) each were given without effect daily for two successive days to eight women, all in the eighth month of pregnancy. It being necessary to cause abortion, one gramme was given daily to one woman for seven days, and to another for three days, without, in either instance, any effect, so that the labor had to be brought on in the usual manner.

On the whole, we believe that the first question must be answered—quinine is incapable of producing abortion during quiet pregnancy.

In answer to the second sub-question, some evidence has already been adduced to indicate that abortion may be so caused, but it is opposed by much stronger facts.

To evidence already quoted may be added the assertion of Walraven[43] that he has frequently seen the exhibition of quinine followed by abortion, the record of two cases of such character by Burt,[44] and no doubt the affirmations of others which we have not seen. Opposed to this, however, is the overwhelming fact that the great body of the profession have for centuries been giving quinine in one form or other to pregnant women indiscriminately, and if abortion had been produced it must have been noted long ago. Further, direct testimony is not wanting. Malaria often induces abortion, and Erwin,[45] James C. Harris,[46] and A. Russwurm[47] testify from personal experience that quinine will arrest abortion from such cause. J. A. Ashford,[48] Beauchamp,* Rooker,* J. S. May,* and A. d'Arcourd have given quinine to hundreds of pregnant women, suffering from malaria, in large doses without disturbing the uterus.

Other testimony might be adduced; but it is incredible, in the face of daily experience, that even the largest therapeutic doses of quinine are abortifacient in malarial fevers or in health.

In regard to the third sub-question,† it seems to us proved that quinine in full doses (ten to twenty grains) is a stimulant to the uterine contractions during labor. The pains it produces so exactly simulate the natural ones as to indicate that they are not so much caused by a specific

* See *American Practitioner*, 1870.

† For details of the evidence the reader is referred to the third edition. Consult also *Practitioner*, xvii., xviii., xix.

action of the drug as by its arousing the general nervous forces of the system. Be this as it may, most of the leading accoucheurs of Philadelphia and of New York are accustomed to rely upon quinine in cases of uterine inertia from exhaustion.*

Voluntary Muscles.—C. G. Sauterson,[49] in a series of experiments upon both cold- and warm-blooded animals, has found that quinine acts directly upon the muscle-fibres, increasing the susceptibility and power of the muscle, but, especially in the cold-blooded animal, causing it to become fatigued more readily than normal.

Nutrition.—Ranke was the first to notice that quinine produces a great decrease in the elimination of uric acid, and thereby provoked many investigators to the making of researches.

Ranke was confirmed by H. V. Bosse[50] and by G. Kerner. The latter observer found that, when about nine grains of quinine were taken in divided doses during the course of the day, the urea was decreased not quite one-eighth, the uric acid to a little less than one-half, the kreatinine was slightly increased, and the nitrogenous material decreased about one-ninth. When a very large dose (thirty-eight grains) was taken in the morning, the urea and the kreatinine were each decreased about one-fourth, as was also the collective nitrogenous material; the phosphoric acid was lessened about one-fifth, and the uric acid about four-fifths. Zuntz (quoted by G. Strassburg[51]) found that twenty-five grains of quinine reduced his elimination of urea nearly forty per cent. A. Schulte also found that 1.8 grammes of quinine depressed the elimination by the kidneys thirty-nine per cent; yet in the experiments of Unruh[52] the action of the alkaloid in depressing urea elimination was not constant, and in the trials of H. Oppenheim[53] the excretion of urea was actually increased. Nevertheless, the experiments, upon the dog, of Rabuteau[54] and of Hermann von Boeck[55] bear strong evidence to the fact that quinine does decrease the elimination of urea.

Considering all the evidence, and especially the rather recent very elaborate studies of Prior,[56] we are warranted in believing it established that *quinine powerfully depresses the elimination of the nitrogenous excretory principles.* That such decrease is due to diminished formation, and not to lessened elimination, seems proved by the fact that in Prior's experiments there was no increase of nitrogenous excretion beyond the normal following the omission of the quinine. It seems, therefore, to be established that quinine has *a direct or indirect depressing influence upon the tissue-changes of the human organism.*

Contrary to what might have been expected, Strassburg, in an elaborate series of experiments, found that quinine had no decided effect upon the elimination of carbonic acid either in healthy or in fevered

* Certain experiments of Wild (*Brit. Med. Journ.*, 1887, ii.) suggest that the quinine may act directly upon the muscle-fibres of the uterine walls. He found that when the solution of quinine sulphate, 1 part to 1000, was brought in contact with the isolated œsophagus of the frog, the œsophagus first shortened, and afterwards lengthened beyond its normal limit, the change probably being, as believed by Wild, due to stimulation first of the weak longitudinal muscular fibres, and later of the more internal stronger circular fibres, as the quinine penetrated the coats. The muscle-fibres of the œsophagus are similar to those of the uterus.

rabbits. These observations of Strassburg are opposed by those of Boeck and Bauer,[57] who found that in cats large doses of the alkaloid cause in the first stage of their action lessened carbonic acid production, but that when the convulsions appear the carbonic acid is increased as the result of the increased muscular activity. R. H. Chittenden[58] found that fatal doses of quinine given to fasting rabbits had no decided effect upon carbonic acid production until just before death, when both the animal temperature and the excretion of carbonic acid fell distinctly. On the other hand, small doses of quinine seemed to cause a gradual falling off in the carbonic acid elimination. Although the evidence is somewhat contradictory, it indicates that any action of quinine upon carbonic acid elimination must be very feeble and uncertain.

THERAPEUTICS.—At present our estimate of the value of quinine in disease, and our knowledge of its therapeutic use, rest solely upon clinical observation, although recent discoveries have enabled us to frame a very plausible explanation of the method by which it overcomes malarial disease.

On account of its power of arresting or preventing putrefactive fermentation by killing the microscopic entities which produce such changes, Binz has recommended quinine in the so-called *septic diseases.*

The chief evidence which he produces is in some ten experiments made upon dogs and rabbits. In each of these experiments two similar animals were poisoned with putrescent liquids, and to one of the pair quinine was freely administered. In two cases the cinchonized animal recovered, while its fellow perished; in three experiments neither of the animals died; and in the other five trials the cinchonized animal lived from two to twenty-four hours longer than the other. These experiments are certainly too few and indecisive to prove in any degree Binz's view. To us they indicate very strongly that quinine has no such influence over the disease as he believes. If living germs in the blood were really the cause of the septic symptoms, and if quinine killed such germs, its action would be as manifest and as unmistakable as it is in intermittent fever.

The results of Binz's experiments seem to us to agree with the emphatic teachings of clinical experience that quinine has no direct specific influence in *pyæmic*, *septic*, or *exanthematous* diseases.

Before the introduction of modern antipyretics the question as to the power of quinine of lowering bodily temperature was extremely important, but at present it is enough to know that as an antipyretic quinine is of very inferior power.

Unless given in enormous toxic doses, quinine does not lower bodily temperature in health. It is alleged, however, by G. Kerner and Jürgensen that it will largely prevent the rise of the bodily temperature which normally occurs from exercise, and it is asserted by various clinicians that it does not affect the temperature in fever. C. Liebermeister[59] came to the conclusion that quinine given in doses of from twenty to forty-five grains in one hour is, in typhoid fever, a very active and certain antipyretic, a conclusion also reached by the Committee of the London Clinical Society.[60]

Naunyn and Quincke[61] found that sometimes quinine prevented the development of fever after the division of the spinal cord in animals, but in other cases failed to do so. Binz[62] has achieved similar results: he says that if the conditions of the fever are too favorably constituted the effect of the quinine fails thoroughly.

The drift of our present clinical evidence seems to indicate that quinine exerts in febrile disease a decided antipyretic action, which is especially manifested during those stages of disease in which the natural tendency is towards a lowering of temperature. In exanthematous diseases, etc., after the use of the cold bath twenty grains of the alkaloid are often efficacious in delaying the return of the excessive fever.

As a simple tonic, quinine is largely used, especially in combination with iron. We are not entirely convinced that it is of much more value in simple debility than is quassia or other simple bitters; but if, as is probable, it be true that quinine lessens to a very great extent the elimination of nitrogen,—*i.e.*, the consumption of tissue,—the general practice is well founded. Hare,[63] as the result of observations made upon himself, believes that quinine has a distinct action in increasing the formation of the red blood-corpuscles. If this be correct, it must have especial tonic value.

When administered in very large doses, quinine, as has been already shown, acts as a powerful depressant, and as such it has been used by Briquet and other French physicians in *rheumatism*. As much as sixty or seventy grains a day have been given, and it is beyond dispute that under the influence of these heroic doses the symptoms of inflammatory rheumatism have often rapidly abated; but the method has found little favor out of France, and is less efficient and more dangerous than other plans of treatment now in vogue. In *inflammatory rheumatism*, after the acute symptoms have abated, when the patient shows evident signs of weakness, especially if there be profuse sweating during sleep, fifteen grains of quinine daily are often of great service.

Conceiving the theory that choreic movements may be due to weakness of the spinal inhibition, H. C. Wood some years ago injected quinine into the veins of choreic dogs, and found that the movements were at once arrested by comparatively small doses of the alkaloidal salts. This led him to make trial of the remedy in the *chorea* of childhood, and as the result of much experience it has been determined that the drug in some cases of this affection is of great value. There are certain cases in which enormous doses are borne without the production of cinchonism: thus, we have given in a month to a child ten years old one thousand grains of the quinine sulphate without causing tinnitus aurium or other disagreeable effect, but with the result of curing a chorea which had resisted all treatment for nearly two years. In our experience in the disease, when there is no tolerance of quinine no benefit is achieved by its administration, but when the quinine is tolerated in large dose its use is commonly most beneficial. Led by the results obtained in chorea, the chief of H. C. Wood's clinic at the University Hospital, Charles S. Potts, con-

ceived the belief that *incontinence of urine* might in many cases be the result of failure of inhibition, and on trial found that very large doses of quinine often put an end to this most annoying symptom, a result which we can confirm from our own experience.

The chief value of quinine is as an *antiperiodic*. There is at present no doubt that the alkaloid does good in all forms of malarial fever by directly affecting the malarial plasmodium or organism.*

Quinine in its relations to *malarial fever* may be considered first as a prophylactic, secondly as a curative agent.

The value of the daily use of quinine to persons exposed to a malarial atmosphere has now been thoroughly tested in all portions of the world. In North and South America, in Europe, in Africa, and in India the prophylactic powers of quinine have been tried on the largest scale in connection with the military and naval services, and the testimony is unanimous in favor of the drug.

A single citation will serve to illustrate this fact.† J. B. Hamilton[67] reports the case of a battery of one hundred and thirty-five men, quartered at Jubbulpore, East Indies, in the same barracks with an infantry regiment. Each of the artillerists received three grains of quinine every other day: to the infantry none was given. The result was that while three hundred out of the five hundred men of the regiment were sick at one time with malarial disease, at no period was more than four per cent. of the battery affected.

The dose of quinine as a prophylactic may be considered as two grains in the morning and three in the evening.

In *intermittent fever*, when there is sufficient time, it may be well to precede the quinine by a mercurial or other purge. If the expected paroxysm be so near that there is not sufficient time for the action of the purgative, the antiperiodic should be administered without previous preparation of the patient. The value of purgatives in obstinate intermittents, as an adjuvant to quinine, is often overlooked, although in some

* At one time it was supposed that the relations of quinine to malaria were in some way connected with its peculiar property of fluorescence, a property which is in turn probably connected with the remarkable power which the alkaloid has of converting the chemical rays of the spectrum into light; or, in other words, of rendering visible the ordinary invisible rays of the solar or other spectrum. When a colorless watery solution of one of its salts is examined, a pale blue line upon the surface is very noticeable; and Stokes has shown that solution of quinine has the power of entirely stopping certain of the rays of light, so that when a beam is transmitted through it to light up a second vessel of the solution this latter displays no fluorescence. H. Bence Jones[64] has found that when the electric light is used this test is so delicate that one grain of the alkaloid may be detected in 1,450,000 grains of water. He has also discovered that man and animals are pervaded by a substance which, in its action on light and in many chemical reactions, very closely resembles, if it be not identical with, quinine. Believing this substance to be probably an alkaloid, he has given it the name of *animal quinoidine*. Edward Rhoads and William Pepper, Jr.,[65] made observations upon ten cases of malarial fever in which no quinine had been used, and have found the fluorescence of the blood to be from 0 to 1½, instead of 3 to 6, which is said to be normal. Chalvet[66] has, however, shown that this fluorescent substance exists in various foods, and is probably of vegetable origin.

† See also K. M. Downie, M.B. (*Indian Medical Journal*, March 1, 1872).

cases the employment of purgatives, and of such diuretics ... with much tartar, seems to be almost essential for the successful use ... periodic.

When there is necessity for prompt action, the quinine ... in a single dose, or in any other method that the circum... case will allow; but ordinarily the best plan is to comm... hibition of the drug about eight hours before the expect... and to continue in hourly doses until from three to four ho... attack is due.

In *pernicious fever*, or *malignant malarial poisoning*, ... be lost after the first paroxysm in getting the patient cin... may be uncertain whether the attack be of the quotidian o... type. At least sixty grains of the alkaloidal salt should b... during the first twenty-four hours; in very severe types ... even larger doses than these are necessary, less than sev... of the drug sometimes being unable to suppress the disea...

In *remittent* or *bilious fever* it may often be advisable ... tives and febrifuges before the quinine. As soon as th... appeared, the exhibition of quinine should be begun. ... tions or even severe cerebral symptoms occurring dur... fever are no contra-indications to the use of the specific. ... exists, other channels of entrance than the stomach shoul... on account of the local irritant action of quinine.

When the symptoms in remittent fever are severe ... continuous, it may be not only proper but necessary for ... life to exhibit quinine freely during the period of fever. ... the alkaloid is probably antipyretic as well as antiperiodic, ... know of any theoretic or clinical objection to its use durin... fever.

In *malarial intermittent neuralgia*, as in all other form... manifestations of malarial disease, quinine is efficient, ... usually necessary to administer it in large doses (thirty to ... intervals).

In *neuralgia* which, although not dependent upon m... the intermittent type, quinine will often temporarily set a... ysmal attacks, and sometimes effect a cure. The same ... stated in broad terms as true of *all non-malarial intermitt...* In the great majority of such cases, unfortunately, the ... quinine is only temporary, and any controlling power is so...

The amount of quinine required in ordinary cases of ... and the method of its administration, have been the subj... endless discussion. As the result of much experience an... are convinced that it is better to use the remedy in large ... tervals than to administer it continuously in smaller amou... climate fifteen grains of quinine a day will usually put an ... intermittent, but the paroxysm will be very apt to recu...

grains of the alkaloid be afterwards given daily for some weeks. We believe it is better to administer from twenty to twenty-five grains in the beginning, sufficient to produce very pronounced cinchonism and to arrest the disease at once. The full physiological effect of the drug should then be maintained for two or three days, and no more of it given except at regular intervals. The paroxysms have undoubtedly a great tendency to return on the seventh day after their arrest, and every seventh day for some weeks full cinchonism should be produced. If the observation of Councilman, that large doses of quinine entirely destroy the malarial organism, be correct, the practice just spoken of has a foundation in scientific as well as in empiric observation.

Local Use of Quinine.—The effect of quinine upon the lower organisms has suggested its local use in various disorders *supposed* to depend upon the presence of such entities. Thus, Henke,[68] finding some peculiar motile cells in the sputa of *whooping-cough*, employed inhalations of quinine with asserted good results. Henke was not, however, the first to suggest either this fungoid pathology of whooping-cough or the use of quinine. Binz[69] in 1870 asserted that quinine had a specific action in whooping-cough, provided it was given in large doses in solution, so as to come in contact with the mucous membrane in its passage through the pharynx; and in 1871 Letzerich[70] announced that whooping-cough was due to a fungus in the lung. Dawson[71] has confirmed the value of the method of Binz; but, if the fungoid theory be—as we do not believe—true, the plan of Henke must certainly be the better one. The use in *hay fever*, as recommended by Helmholtz, of a weak tepid solution (one to three grains to one fluidounce), as nearly neutral as possible, freely applied to the nasal mucous membrane, has not achieved general recognition, and any influence which the alkaloid has in either whooping-cough or hay fever probably depends on its direct influence upon the mucous membranes. In the later stages of *gonorrhœa* the topical employment of its solution (five to ten grains to one fluidounce) is often serviceable.*

ADMINISTRATION.—Owing to its bitter taste, quinine sulphate is generally given in pill, which may be made with gum, or simply by adding a little sulphuric acid to the alkaloidal salt and quickly rubbing up the pasty mass into pills before it hardens. When a rapid action is desired, the quinine should be given in powder, or in solution made by adding a drop of dilute sulphuric acid for every grain of the salt. In the use of pills of quinine, care should be exercised to see that they are soft and fresh, for when old and hard they not infrequently pass through the bowels unchanged. The ready-made "sugar-coated" pills kept in the shops should be avoided, as uncertain in their action: indeed, capsules containing quinine in powder are always preferable to the pill.

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* Walerian Sokolow affirms that the local application of quinine to *wounds* has a very remarkable effect upon the granulation tissue, a similar effect being produced by the administration of the drug by the mouth. (For details, see *Inaug. Dissert.*, 1891, abstracted in *Schmidt's Jahrb.*, 1892.)

When quinine sulphate is given *hypodermically* it acts with much greater promptness and apparently with greater force than when administered by the stomach. Albertoni and Ciotto[72] found that when they injected it into the jugular vein it failed to appear in the bile, but when they administered it by the mouth it was freely eliminated with that secretion. Biliary salts of quinine are so insoluble that their reabsorption must be effected, if at all, very slowly: hence possibly the superior efficiency of the hypodermic method. The local irritant action of quinine, however, forbids its hypodermic employment except in cases of emergency. Given in this way, it very generally produces great local disturbance (abscesses, ulcers, etc.), and in several cases is alleged to have caused fatal tetanus.[73] When it is so given, care should be taken to have *an excess of acid* (tartaric is the best) in the solution, to prevent precipitation of the quinine by the alkaline juices of the cellular tissue. *Quinine Bisulphate* (QUININÆ BISULPHAS, U. S.) is soluble in ten parts of water, and should be preferred for hypodermic use: even its solution should be slightly acidulated. Ten grains of quinine injected under the skin are probably equivalent to fifteen grains given by the mouth.

Contra-indication.—On account of its irritant properties, quinine must be used with caution when there is irritability or inflammation of any part of the gastro-intestinal tract. It is strongly contra-indicated by inflammation of the middle ear, and may greatly and permanently increase dulness of hearing. The statement of M. Friedmann[74] that ergotin, and that of W. B. Dewees[75] that chloral greatly lessens the tinnitus aurium produced by quinine and salicylic acid need confirmation. Irritability of the bladder or other portion of the genito-urinary tract contra-indicates the use of quinine: hence it is often badly borne by old men. It is even asserted that it will in some persons cause hæmaturia.*

TOXICOLOGY.—The general symptoms produced by toxic doses of quinine have been sufficiently discussed. Owing to personal peculiarities or idiosyncrasies, quinine sometimes causes manifestations entirely unlike those ordinarily seen. Thus, in a case reported by A. Erlenmeyer,[76] the

* In certain regions of country persons suffering from malarial poisons have intermittent attacks of hæmaturia, or probably, to speak more correctly, of methæmoglobinuria, in which the hæmaturia has been attributed by many practitioners to the influence of the quinine sulphate. The facts, however, that quinine never produces methæmoglobinuria in healthy individuals, that the attacks are accompanied by chill, fever, and sweat, following, according to Carreau, absolutely the course of the paroxysm of intermittent fever, and that, though quinine is used everywhere, the methæmoglobinuria occurs only in certain localities, certainly seem to prove that the attacks are really due to a peculiar form of malaria and not to the quinine. The most elaborate account we have met with is that published in Guadeloupe, in 1891, by J. Carreau (*La Méthémoglobinurie Quinique*, 1891; see also *Bull. Soc. de Méd. Pratique de Paris*, 1891; *Arch. de Méd. Navale*, 1896, lxv., 1897, lxvii.; *Bull. Thérap.*, xcvii.); Pispiris (*Le Progrès Méd.*, 1891, xix.) affirms that in some cases of malarial fever not only the internal administration but also external friction of the quinine sulphate will provoke serious gastro-intestinal hemorrhage. It does not, however, appear probable that the quinine in his cases was the cause of the bleeding.

symptoms simulated those of strychnine-poisoning.* In some persons a few grains of quinine given internally produce wide-spread erythema and subdermal œdema, affecting it may be the whole body, but usually most pronounced in the face, and accompanied by pronounced disturbances of the nervous system and circulation, the symptoms usually subsiding in from a few hours to a few days, and sometimes being followed by desquamation of the cuticle.

The importance of these idiosyncrasies was shown in a case in our own practice, in which two grains given by the mouth produced a furious general urticaria, with great subdermal swelling and cardiac depression of the most alarming character; according to B. D. Titlow,[77] violent general erythema involving the lymphatics was produced by one-third of a grain of quinine. Miccichè[78] reports the death of an adult caused by the hypodermic injection of seven and seven-tenths grains (one-half gramme), the symptoms being great paleness of the surface, small, frequent pulse, high fever, severe nervous depression, increasing stupor with delirium, great dyspnœa, jaundice, hæmaturia, and anuria. Death occurred on the seventh day. Both during life and at the autopsy the evidences of great destruction of red blood-corpuscles were apparent. Purpura has also been ascribed to the alkaloid.[79] Chevallier[80] describes a peculiar affection of the skin, etc., as occurring among workers in the bark.

Fatal instances of poisoning by quinine are rare in literature, but Husemann[81] has made a collection of cases in which death has been attributed to the alkaloid,—not always, in our opinion, with correctness. The minimum fatal dose is not known, but must be very large.

Clapton[82] details a case in which a soldier took at one dose an ounce of the sulphate, stirred up in some water, without the induction of any more serious symptom than a mild stupor; a similar case is mentioned by Lente, on the authority of Woodhull; and a third is recorded by Taussig.[83] R. G. Wharton[84] records a case in which during thirty-six hours a half-ounce was taken without vomiting and without ill effect. We cannot help suspecting that in all of these cases much of the drug passed through the intestines without absorption. In the famous case of Bazire, five ounces taken in the course of ten days caused death.

Quinine Hydrobromate (QUININÆ HYDROBROMAS, U. S.) is soluble, at 59° F., in fifty-four parts of water and in 0.6 part of alcohol. It is stated that a ten per cent. solution in a mixture of twenty-five parts of alcohol and seventy-five parts of water is not irritant when used hypodermically.

Quinine tannate,† although not official, has been used to some extent, and is not altogether inefficient. It has the great advantage of not being disagreeable to the palate, but is less active and less certain than the more soluble salts of the alkaloid, and is also much slower in its operation.

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* For cases, see *Brit. Med. Journ.*, 1869, ii.; *Berlin. Klin. Woch.*, 1877, 294; *Phila. Med, Times*, x. 166; *N. Y. Med. Record*, xxi. 627.

† For an elaborate discussion of the therapeutic value of this salt, see *Bulletin de l'Académie*, Paris, 1872.

If given at all, it should be in doses one-third greater than those of the sulphate.

The *double bimuriate of quinine and urea*, although not official, has been used to a considerable extent for hypodermic injections. It is said that a fifty per cent. watery solution, when thrown into the cellular tissue, produces very slight local irritation. It contains about sixty-one per cent. of the alkaloid, and is capable of producing cinchonism.

QUINIDINÆ SULPHAS. U. S.—*Quinidine sulphate* occurs in long, shining, silky, acicular crystals, soluble in one hundred parts of water at 59° F., in seven parts at 212° F., readily soluble in alcohol, nearly insoluble in ether. It is a basic salt, like the quinine sulphate, readily taking another equivalent of acid. It behaves like its isomer with chlorine and ammonia, but is distinguished by rotating light powerfully to the right instead of moderately to the left. It probably closely resembles quinine in its physiological and therapeutic properties, and is an efficient antiperiodic: the dose is about one-third larger than that of quinine.

CINCHONINÆ SULPHAS—CINCHONINE SULPHATE. U.S.

The pure alkaloid cinchonine crystallizes in prisms and needles. The official cinchonine *sulphate* is in short oblique prisms of a very bitter taste, soluble, at 59° F., in sixty-six parts of water, more freely in boiling water, readily soluble in alcohol.

PHYSIOLOGICAL ACTION.—Conzen (quoted by Husemann) has found that the action of cinchonine on infusoria and on fermentation is similar to but weaker than that of quinine, and that on the movements of the white blood-corpuscles its influence seems transient. Laborde[85] states that pure quinine does not cause epileptiform convulsions in the lower animals, although commercial quinine does so on account of its impurity, and that in poisoning with cinchonine violent epileptiform convulsions are a chief symptom. Bochefontaine[86] affirms, however, that quinine does convulse, although less actively than does cinchonine, which latter alkaloid he found to vomit less than quinine. According to Johnnsen, the effect of cinchonine upon the elimination of urinary solids is even more powerful than that of quinine. It is eliminated unchanged, appearing in the urine in half an hour, and disappearing after massive doses only in ninety-six hours,—the great bulk being thrown off in the first twenty-four hours. In Bochefontaine's experiments the relative strength of cinchonine to quinine was about 10 to 16, in Bernatzik's (on dogs only) as 4 to 5. De Schweinitz has found that cinchonine produces amaurosis in the dog, as does quinine.

THERAPEUTICS.—As an antiperiodic, cinchonine exerts a similar influence to quinine, but is probably about one-third weaker than that alkaloid, and must be used in correspondingly larger dose. J. B. Hamilton affirms as the result of experiment that cinchonine as a prophylactic

against *malaria* is even superior to quinine. As a tonic we have never been able to perceive that cinchonine acts differently from quinine.

CINCHONIDINÆ SULPHAS. U. S.—*Cinchonidine sulphate* occurs in white, silky, lustrous needles or prisms, odorless, of a very bitter taste, soluble in seventy parts of water, freely soluble in acidulated solutions. It polarizes to the left, and is not fluorescent. G. Sée and Bochefontaine found that the lethal dose of cinchonidine for the frog is 0.015 gramme; for the dog, 2.5 grammes. The symptoms in the dog are general feebleness, titubation, increase of pulse-rate and arterial pressure, vomiting, salivation, convulsions,—less severe than those caused by quinine,—great loss of muscular power, stupor, fall of arterial pressure and of temperature, and death from arrest of respiration.[87] A boy aged five years took one hundred and twenty-eight grains in solution during six hours without vomiting. There were then convulsions followed by great collapse, fall of temperature, pulselessness (with seventy-four cardiac beats per minute), dilated pupils, muscular relaxation, and, finally, death; consciousness was preserved to the end.* It is evident that this alkaloid closely resembles its congeneric alkaloids in its action upon the human organism. Clinical experience has proved it to be a reliable tonic and antiperiodic. According to Byasson, it is eliminated by the kidneys unchanged. It has been asserted that it produces less disagreeable symptoms, both gastric and cerebral, than does quinine; but Rafferty, who has administered three hundred ounces of the sulphate, affirms that it is more apt to cause nausea and vomiting. The dose is one-third greater than that of quinine. De Segrais[88] has found the *bromohydrate* given hypodermically in doses of four to six grains (0.26–0.4 Gm.) very efficacious.

CHINOIDINUM.—*Chinoidin*, or *Quinoidin*, is a blackish substance, with an almost resinous fracture, which is obtained by the evaporation of the mother-liquor after the crystallization of the alkaloids out of it. This substance contains probably amorphous quinine and cinchonine, besides quinidine and cinchonidine. It is a very cheap, efficient antiperiodic in doses of about twice those of pure quinine. It should be given in pill or capsule.

The INFUSUM CINCHONÆ (six per cent., U. S.), dose, a wineglassful; the tincture (TINCTURA CINCHONÆ—twenty per cent., U. S.), dose, one to two teaspoonfuls (4–7 C.c.); the fluid extract and the solid extract (EXTRACTUM CINCHONÆ FLUIDUM, U.S., and EXTRACTUM CINCHONÆ)—the doses of which are five to fifteen drops (0.3–1 C.c.) or grains respectively—are all of them useless preparations. The compound tincture (TINCTURA CINCHONÆ COMPOSITA—ten per cent., U. S.—*Huxham's Tincture*), as a tonic, is the best preparation of the bark, and is a very elegant remedy in convalescence, in doses of one to four drachms (4–15 C.c.).

* See *N. Y. Med. Journ.*, 1884, xxxix.

CINCHONAMINE.—This alkaloid was discovered by Arnaud[89] in the Cuprea bark from Colombia, probably the product of Remijia pedunculata and Remijia Purdieana. Its physiological action has been partially investigated by Sée and Bochefontaine.[90] In poisonous doses it produces violent convulsions in the dog, with fall of the arterial pressure. It also arrests the heart in diastole, and increases especially the secretion of the salivary glands. Its influence upon man has not, so far as we are aware, been studied, but its botanical and chemical relations make it probable that it resembles quinine in its physiological and therapeutical properties.

WARBURG'S TINCTURE.—This is a dark brown liquid, prepared in accordance with a very complicated formula,* which has obtained an extraordinary reputation in India and other tropical countries in the treatment of severe *remittent* and malignant *malarial fevers*. The testimony is so strong as to its remarkable and almost certain efficiency that it cannot be questioned, and entitles the tincture to rank above all other remedies. The method of administration is as follows. The bowels having been freely opened, a half-ounce of the tincture is given undiluted, all drink being withheld, and at the end of three hours a second half-ounce is in similar manner exhibited. Soon after the last dose a profuse and very aromatic perspiration sets in, and convalescence is usually secured. The remedy is also commended in one-drachm dose in acute *nervous exhaustion* and *collapse* without organic disease.

EUCALYPTUS. U.S.

Of the Australian genus Eucalyptus,† which comprises about one hundred and thirty-five species of evergreen trees, the U. S. Pharmacopœia recognizes only E. globulus, whose leaves are official, but allows the oil of

* For formula, see *United States Dispensatory*, 18th ed.

† Attention was first called by Labillardière in 1792 to the value of the Eucalyptus globulus, but it was not until 1860 that M. Ramel commenced the culture of the tree in Paris and induced the Prefect of the Seine to order its cultivation on a large scale. Since that time it has been largely introduced into Europe, Algeria, South Africa, and California, and in some of these countries planted forests are now growing and spreading. The tree is remarkable for combining extreme hardness of wood with a rapidity of growth asserted to be about five times that of our ordinary trees; it is even affirmed that shingles made of it are fire-proof. Its capability for absorbing and evaporating water is extraordinary, and to it has been attributed the freedom of Australia from malarial climatic influences. Indeed, it is stated that a tree will evaporate ten times its weight of water in twenty-four hours, and numerous examples are given in which swamps in Europe and Algeria have been rapidly converted by it into dry ground. It is believed to destroy malaria not only by draining the soil, but also by yielding balsamic exudations to the air; however this may be, there is at present very strong evidence as to its power of rendering infected districts healthy. As, however, the consideration of this belongs to the subject of hygiene rather than of therapeutics, the reader is referred for detailed information to the following memoirs: Regulus Carlotti (*L'Eucalyptus, son Rang parmi les Agents de la Matière Médicale*, Ajaccio, 1872), M. Gimbert (*L'Eucalyptus Globulus, son Importance en Agriculture, en Hygiène, et en Médecine*, Paris, 1870), Waterer (*Bulletin de la Société d'Acclimatation*, 1872; *London Medical Record*, Dec. 1873; *London Lancet*, 1877, ii.).

Under the name of *Eucalypsinthe*, a liqueur distilled from the leaves of the eucalyptus has appeared in European commerce.

eucalyptus (OLEUM EUCALYPTI, U. S.) to be distilled from fresh leaves of various species of the genus. Neither the dried leaves nor their fluid extract (EXTRACTUM EUCALYPTI FLUIDUM, U. S.) are themselves used in medicine. From the various species of Eucalyptus are prepared in Australia a number of volatile oils, and also the *Eucalyptus Gum* of the British Pharmacopœia, the so-called *red gum*, which occurs in commerce in grains or masses scarcely to be distinguished from ordinary kino, contains nearly five per cent. of tannic acid, and is much used as an astringent, especially in the form of lozenges.

Most of the eucalyptus oils are composed very largely of eucalyptol or of phellandrene. The oils containing *phellandrene* were thrown out by the revisers of the U. S. Pharmacopœia, evidently under the impression that the active physiological portion of the oil is eucalyptol. Concerning the physiological action of phellandrene, however, we have no knowledge.

Oil of eucalyptus is a colorless or faintly yellowish liquid, having a characteristic somewhat camphoraceous odor and a spicy, disagreeable taste. Dose, ten to fifteen minims (0.6–0.9 C.c.), in capsules. Its active principle (EUCALYPTOL, U. S.) is to be preferred to the oil as more concentrated and uniform in action. Dose, five to ten minims (0.3–0.6 C.c.). All the virtues of Eucalyptus probably reside in the volatile oil, which is in greatest abundance in the leaves.*

PHYSIOLOGICAL ACTION.—*Local Action.—Absorption and Elimination.*—The oil of eucalyptus is decidedly irritant, large doses producing burning in the mouth and fauces, with increased secretion of saliva, followed very soon by a feeling of warmth in the stomach. It is absorbed from the alimentary canal, and is probably eliminated by the lungs, skin, and kidneys. In the experiments of Binz, the day after the ingestion of seventy-five drops the breath smelt of the drug and the perspiration of amylic alcohol; the urine began to have the odor of the oil an hour and a half after its ingestion, and continued to have it for thirty-six hours. Gimbert[1] states that the odor imparted to the urine resembles that of violets, and is very similar to that caused by turpentine. Binz affirms that upon the lower infusoria the oil acts even more powerfully than does quinine, and its antiseptic properties are without doubt great (Gimbert).

General Effect.—The general effect of the same dose of the oil appears to vary considerably in different individuals; but the following summary comprises the facts as nearly as may be. After the ingestion of from ten to twenty minims, a period of mental and physical activity is often apparent, followed by a feeling of calm and serenity. By larger doses, or in susceptible persons by the doses mentioned, there is caused disturbance of the digestive organs, ending often in loose stools having the odor of the oil, with augmentation in the frequency and force of the

* It has been affirmed that the leaves of Eucalyptus contain also an alkaloid; but Rabuteau (*Bull. Thérap.*, lxxxiii. 549) has demonstrated that this is an error.

pulse. Gubler adds to these symptoms an elevation of temperature; but in Gimbert's experience febrile manifestations, although occasionally occurring, were not usually present. In some cases the medicine acts very disagreeably, producing violent cardiac palpitations or intense headache: how far these are directly dependent upon the drug, or are sympathetic upon its local action on the stomach, is uncertain. If the dose be repeated, or if a larger amount be taken at once, a period of sedation manifests itself; the pulse loses its force, and the animal temperature is abated. After doses of seventy-five grains, Binz noted numbness of the limbs, with a feeling of excessive weight in them. If the use of the remedy be persisted in, a state of asthenia is induced; the temperature falls as much as a degree and a half, and the pulse even to 50 (Gimbert): the respiration becomes less frequent, and the muscular weakness extreme, so that raising the arm to the mouth is painful; the sensations are blunted, but the intellect is absolutely unaffected.

In an old man who took eighty drops, the power of motion almost disappeared; the man also affirmed that he lost for the time being all sense of the presence of his limbs, so that he was unconscious of possessing them when he shut his eyes, although his intellect was perfectly clear throughout. In a case reported by Alfred Neale,[2] a little over half an ounce of the oil of eucalyptus is said to have produced death in fifteen hours in a healthy boy: the only recorded symptoms were violent dyspnœa with collapse.*

Upon the lower mammalia the oil of eucalyptus appears to act precisely as it does on man. According to the experiments of Gimbert, the hypodermic injection of the oil is immediately followed by a period of excitement, seemingly in great measure due to the intense local irritation; after about half an hour, if the dose has been sufficiently large, the animal begins to stumble and totter in walking, the breathing grows more and more slow and irregular, the limbs give way, the ears droop, the muscular weakness becomes profound, and death, preceded often by partial convulsions, occurs through failure of respiration.

Death appears to be produced by the fatal dose through asphyxia. According to the experiments of Gimbert (confirmed by Binz), the motor nerves and the muscles are not affected, so that the failure of motion and reflex activity is probably due to a depression of the motor side of the spinal cord and of the medulla. According to Hermann Schläger, the hypodermic injection of the oil produces a temporary rise of temperature, probably as the result of the local irritation, but after toxic doses the temperature falls decidedly. Schläger[3] also states that the large dose of the oil causes a marked lessening of the arterial pressure, whose coming on is not affected by previous section of the vagi, by atropinization of the heart, or by section of the cord. It would, appear, therefore, that the oil of eucalyptus directly depresses the heart or the peripheral arteries. As in Schläger's experiments the force of the isolated frog's heart

* As a quart of very bloody serum was found in the pleural cavity, and as the boy was not seen professionally until he was *in articulo mortis*, much doubt attaches to this case.

was distinctly depressed by the drug, the latter must be a direct cardiac depressant.

Mosler [4] affirms that in dogs whose spleens were exposed, injections of tincture of the leaves of eucalyptus produced a decided contraction of the viscus. According to Gimbert, the excretion of urea is enormously increased by the use of the drug.

THERAPEUTICS.—The oil of eucalyptus has some power as an antiperiodic, but is certainly very much inferior to the cinchona alkaloids, and should be used only in cases in which for sufficient reasons these alkaloids cannot be employed, or as an adjuvant to them.

Joseph Keller [5] used it in four hundred and thirty-two cases, of which two hundred and ninety-three had suffered from previous attacks. Of the tertians 75.57 per cent., of the quartans 70 per cent., and of the quotidians 67.89 per cent. yielded to the remedy. He recommends it as especially valuable in obstinate cases in which quinine has been taken again and again. Lorinser,[6] Haller,[7] Bohn,[8] Carlotti, Cortan,[9] Gimbert, Gubler, Tristany,[10] of Spain, J. H. Musser,[11] and others bear testimony to the power of eucalyptus in malarial diseases; while Brudell,[12] Seitz,[13] and Papillon [14] affirm it to be of little or no value.

Eucalyptol is also one of the best stimulating expectorants that we possess: in both *acute* and *chronic bronchitis* it may be exhibited when there is free secretion. Children bear it very well.

ACIDUM PICRUM—PICRIC ACID.*

The non-official *Picric* or *Carbazotic Acid* occurs in pale yellow, shining scales. In the pure state it is corrosive, and is therefore used only internally in the form of a salt, the *ammonium picrate* being commonly preferred.

According to Erb,[1] fifteen grains of the ammonium picrate caused in man yellowness of the conjunctiva, skin, and urine, sometimes but not always accompanied by marked gastric disturbance. The acid is evidently rapidly absorbed and may be found abundantly in the urine. A teaspoonful produced no more violent symptoms in a man than severe vomiting and purging.[2]

Binz [3] has found that picric acid exerts upon the infusoria an influence similar to, but much feebler than, that of quinine. Von Beck [4] reports urticaria and measles-like eruptions produced by the prolonged use of the ammonium picrate.

W. Erb found that the daily use of a grain (for ninety days) of a picrate produced, in a rabbit, yellowness of the conjunctiva, of the inner surface of the ear, and of the urine, with an occasional slight diarrhœa and great loss of weight, without fever. Three grains a day caused, in about two weeks, the death of the rabbit, with symptoms of inanition. All the tissues, except the nervous, were stained of

* Picric acid scarcely belongs in this chapter, but, as it has attracted most attention as an antiperiodic, in the ignorance which exists as to its physiological action we have here introduced it.

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FAMILY V.—ANTIPYRETICS.

ACIDUM CARBOLICUM—CARBOLIC ACID. U.S.

Phenic Acid, *Phenylic Alcohol*, is a substance obtained from coal-tar by distilling at a temperature of between 300° and 400° F., adding to the distillate a hot concentrated solution of potassa, and, after this, water, separating the light oily matters which rise to the top, and adding muriatic acid to the heavy alkaline bottom layer, when impure carbolic acid separates. This impure carbolic acid (ACIDUM CARBOLICUM CRUDUM, U. S.) is of a dark color, and contains several congeneric bodies, especially xylic and cresylic acids.* For disinfectant purposes these appear to be at least of equal value with the carbolic acid, and therefore the crude product of the above-detailed process is very largely used. Carbolic acid occurs at ordinary temperatures in minute, colorless, transparent plates, or long rhomboidal needles, often fused into a mass, having a hot, corrosive, peculiar taste and odor, resembling but decidedly different from those of creosote. If, on exposure to the air, phenic acid becomes brown, it contains impurities. When opportunity is afforded, solid carbolic acid absorbs water from the atmosphere and melts into an oily looking, colorless liquid. It is inflammable, neutral to test-paper, but combines with bases; soluble in about twenty parts of water, very soluble in alcohol, acetic acid, ether, glycerin, and the volatile and fixed oils. Nitric acid converts it into picric acid.

PHYSIOLOGICAL ACTION.—*Local Action.*—In concentrated form carbolic acid is a mild escharotic, its momentary application to the sound skin producing burning pain and a white discoloration which changes to a reddish stain, gradually fading away as the skin desquamates. If the application be prolonged an eschar forms.

Carbolic acid in sufficient concentration is poisonous to all forms of

* *Cresol*, *Cresylol*, or *Cresylic Acid*, boiling at a temperature higher than carbolic acid, is a later product of the fractional distillation of coal-tar. It is undoubtedly a very powerful antiseptic, and Henri Delplanque (*Thesis*, Paris, 1888) affirms that it is much stronger in its germicidal influence than is carbolic acid, and only one-quarter as strong as a poison to the higher animals. It forms with sulphuric acid a compound which is odorless, soluble in water, and, according to Fränkel (*Zeitschr. f. Hygiene*, 1889), scarcely irritating, a four per cent. solution being readily retained in the mouth. The experiments of Fränkel have led him to the conclusion that *cresol-sulphuric acid* is much more powerful as a disinfectant than is carbolic acid. If these conclusions be correct, cresol is especially valuable in practical medicine; but in view of the cases reported by Faust (*Jahresb. d. Gesellschaft f. Natur und Heilkunde*, Dresden, 1895-98), the comparative innocuousness of cresol seems to be very doubtful.

protoplasm ; thus, even its weak solution arrests the movements in ciliated cells and in white blood-corpuscles (T. M. Prudden,[1] Labée[2]). It appears, however, to act especially upon the central nervous system and upon the peripheral nerve-endings ; as was simultaneously pointed out by Erasmus Wilson[3] and J. H. Bill,[4] it is capable of acting as a local anæsthetic. Its solutions are actively germicidal.

In 1870 Grace Calvert proved that albumin was preserved for eleven days when mixed with carbolic acid, and John Dougall that one-twenty-five-hundredth part would destroy spermatozoa and the higher infusoria. Schroeter, in 1878, determined that 0.0501 per cent. (1 in 2000) would keep flesh for four weeks, and 0.2 per cent. permanently. It was soon found that the acid acted even more powerfully upon moulds than upon putrefactive organisms. The first to study the action of carbolic acid upon vaccine lymph were Braidwood and Vacher, and their experiments have been repeated and extended by Dougall, by J. W. Miller, by Hoppe-Seyler, and by Baxter. Each of the last two observers found that two per cent. of the carbolic acid destroyed with certainty the infective power of vaccine, a conclusion, on the whole, not discordant with that of the other observers. The germicidal power of the drug has also been studied by Hugge, Rosenbach, Baxter, Sternberg, Davaine, Koch and Blyth, Arloing, Cornevin, Thomas, and various other observers, upon almost all the known forms of infective organisms.

The concordant testimony of experimenters* shows that one per cent. in an aqueous solution will destroy with certainty the virulence of ordinary septic and purulent matters, of the tubercle bacillus, and of the micrococci of fowl-cholera ; some of the organisms related to putrefaction are also destroyed by solutions of this strength, but to produce these results with certainty the contact must be continued for many hours. Two per cent. of the acid in an aqueous solution is required to destroy the infection of vaccine or of glanders.

As a vapor, carbolic acid seems to act very feebly as a disinfectant or germicide, and it is very evident that the popular estimate of the value of carbolic acid has been too high.

Absorption and Elimination.—Carbolic acid is readily absorbed through the gastro-intestinal mucous membrane as well as through the skin. Hoppe-Seyler[5] found it in the blood, where it probably circulates as an alkaline carbolate and also uncombined. It is rapidly eliminated, having been found in the urine by Almén,[6] by Patrouillard,[7] by Salkowski,[8] by Hoppe-Seyler, by Waldenström,[9] and by Hauxmann[9]: Hoppe-Seyler detected it in the saliva, and it is probably eliminated in all the secretions. The researches of Baumann,[10] which have been substantially confirmed, show that the carbolic acid is changed into a peculiar sulphocarbolic acid, a sort of ether-sulph-acid, having the formula $C_6H_5O.SO_2.OH$, which finally unites with alkalies and is eliminated as a sulphocarbolate ; when

* There are, it is true, some experiments which seem to be discordant with these results, especially those of Notter and of Jalan de la Croix, who found that as much as ten to thirty per cent. of the acid was necessary to prevent the movements of bacteria in putrid infusions of beef; but there was probably some error in their experimental methods.

large quantities of the acid are administered, some of it escapes unchanged.

In a fatal case of poisoning Patrouillard obtained an oily fluid, believed to be pure carbolic acid, by shaking the urine with ether, allowing the mixed fluids to separate, and removing the ethereal layer and evaporating.

Although, as stated, carbolic acid is to some extent eliminated from the system, a portion of it is burnt up in the body. The black coloring-matter of the characteristic urine of carbolic acid poisoning is in all probability an *educt from carbolic acid*, formed by its partial oxidation.

Hauxmann has proved that this black coloring-matter is not altered hæmatin or any fixed coloring-principle, by finding that the urine is cleared up by heating after the addition of an acid; and his conclusion is corroborated by the observation of Stevenson,[11] of Guy's Hospital, who found that the black urine does not contain more than a normal proportion of iron. When carbolic acid is oxidized outside of the body, as by the action of potassium permanganate, oxalic acid is formed; and Salkowski has found that when phenic acid is given to animals oxalic acid appears in the urine. Other observers have, however, failed to detect these oxalates. Fr. Schaffer,[12] A. Uerbach,[13] and E. Baumann and C. Preusse[14] found that the phenol was at least in part oxidized into *hydrochinone* and partly into a greenish-black substance upon which the coloring of the urine seems to depend. The researches of L. Brieger[15] led him to the conclusion that when carbolic acid is taken in not too large quantities a portion of it unites with sulphuric acid and a portion of it is converted into various colored oxidation products, some of which are very poisonous. According to the experiments of W. Kochs,[16] this change occurs in the large abdominal glandular viscera.

Schmiedeberg[17] has come to the conclusion that no phenol is oxidized in the body, but that it is all eliminated in combination with sulphuric acid, or to a less extent with glyco-uronic acid. The evidence is, however, too strong against this view, and the true conclusion seems to be that when carbolic acid is taken *in great excess it is in part eliminated as carbolic acid*, and that the remainder of it (the whole of it when taken in moderate amount) *in part escapes in combination with an alkali as sulphocarbolic and glyco-uronic acids and is in part oxidized in the system.* Reale[18] affirms that when the sulphuric acid has all been appropriated phosphoric acid is attacked by the phenol and a phospho-carbolate formed.

Production of Carbolic Acid in the Animal.—Städeler[19] discovered that when sulphuric acid was freely added to cow's urine the latter yielded upon distillation carbolic acid, and concluded therefrom that normal urine contains carbolic acid. He has been corroborated by Buliginsky[20] and by Hoppe-Seyler;[21] so that phenol is certainly a constituent not only of the urine of cattle, but also of that of men, dogs, horses, and probably other animals. Baumann has succeeded in producing carbolic acid out of fibrin by a protracted digestion with the pancreatic glandular substance, and Nencki and Brieger have found that it is constantly present in normal

human fæces. It is probable, as asserted by Salkowski, that the acid is formed in the organism as a late product of the pancreatic digestion. Its elimination by the urine is enormously increased in ileus (one-hundredfold, Salkowski), and diminished in anæmia, phthisis, scorbutus, scrofula, and cancer (Brieger). Hoppe-Seyler's theory, that the acid does not pre-exist in the urine, but is formed out of indican during the processes employed for separating it, is not tenable. It appears to be formed from the albuminous substances, tyrosine being an intermediate product, since Brieger has found that the taking of large doses of tyrosine is followed not by elimination of tyrosine, but by a great increase of the urinary phenol. It is quite possible that the phenol is formed in the intestine by fermentative changes, as Baumann has noticed the closely allied substance indol produced by the putrefactive changes in a mixture of albuminous substance with a small quantity of pancreas and a little ammonium carbonate.* In this connection it is interesting to note that Christiani[22] has not been able to find phenol in the urine of chickens fed upon vegetable diet, although a notable amount is present when a flesh diet is allowed. In a series of experiments I. Munk[23] obtained three grammes as the average excretion of twenty-four hours from a horse.

General Effects.—The largest therapeutic doses of carbolic acid produce no distinct symptoms. Reserving the details as to the effects of toxic doses for the section on Toxicology, it is sufficient for our present purpose to state that the prominent symptoms induced by lethal doses are disturbance of respiration, stupor deepening into coma, rapid, feeble pulse, muscular weakness, abolished reflexes, collapse, fall of temperature, and albuminous or bloody urine, ending in death from central paralytic asphyxia. In some cases convulsions occur.

According to Isidor Neumann,[24] to Ernest Labée, and to Salkowski, a poisonous dose of carbolic acid causes in the frog a paralysis which usually affects first the hind legs,† but eventually spreads to the front legs and involves all parts of the body. After a time there are developed tetanic convulsions, which are apparently reflex in their nature, and are said to be excited by external stimuli or irritations.

Upon mammals carbolic acid acts in very much the same way as it does upon the batrachian. According to W. Kempster,[25] in the mouse and rat it causes intense muscular weakness, followed by violent convulsions and stupor. In the rabbit (Neumann, Salkowski) phenylic alcohol produces muscular weakness, often accompanied by tremblings and restlessness, at last giving place to violent convulsions. As has been pointed out by Turtschaninow,[26] the tremors first commence as peculiar tremulous contractions of isolated muscles, and then of muscle-groups which are irregular, and not at all symmetrical. Early in the poisoning the respiration is affected; and death, which usually occurs in the midst of convulsions, is owing to a *paralysis of the respiration*, since in acute cases the heart is found beating continuously immediately after death. According to the researches of Jules Lemaire,[27] in the dog symptoms very similar to those detailed above are caused by lethal doses of the drug; and Husemann[28] states that in mammals and

* See *Pflüger's Archiv*, xii. 862.

† According to Lemaire, when a frog is allowed to swim in water impregnated with carbolic acid, the front legs are the first affected.

in birds the characteristic phenomena of carbolic acid poisoning are clonic convulsions, sinking of the temperature, diminution of sensibility, dyspnœa, free salivation and secretion of tears, keratitis, and conjunctivitis. According to the latter authority, albuminuria and hæmaturia are occasional phenomena.

Carbolic acid, being a universal poison, acts upon the whole system ; so that the detailed study of its physiological effects when given internally is simply an endeavor to determine what tissues are most susceptible to its influence.

Nervous System.—The influence of carbolic acid on the cerebrum is not very intense in the lower animals, but in the higher species, and especially in man, results in the early production of stupor.

The convulsions are not peripheral, since they do not occur in a limb whose connection with the spine has been severed by division of the nerve, and do take place in a leg which has been protected against the local action of the poison by tying the artery (Salkowski, Labée). They are, therefore, either cerebral or spinal. Although there is a distinct conflict of evidence, it seems established that the convulsions are of *spinal origin.*

Labée and J. R. Haynes failed to get them after section of the cord, but in the far more numerous experiments, upon frogs and mammals, of Salkowski, of Berb and Jogel,[29] of J. S. Stone,[30] and of T. Gies,[31] convulsions occurred after destruction of the medulla, section of the cord, and other operative procedures separating the brain from the lower nervous system. The failures of the first-named experiments are explainable by the facts that the paralyzing influences of carbolic acid are usually first manifested upon the hind legs, and that very large doses of the acid were employed.

The spinal convulsions are accompanied by increased reflex activity, which is lost as the paralytic state is reached, so that carbolic acid appears *first to stimulate and then depress the spinal centres.* Stone asserts that the stimulation is preceded by a primary depression, due to stimulation of Setschenow's inhibitory centre in the medulla.

In carbolic acid poisoning the nerves and muscles are not distinctly paralyzed (Salkowski, Hoppe-Seyler), but the very careful experiments of Gies have proved that the muscles are less sensitive and more easily exhausted than is normal.

Circulation.—The action of carbolic acid upon the heart is not a very marked one, but there can be little doubt that in sufficient amount the drug *depresses the heart.*

After death from acute poisoning the heart is usually found to be beating regularly (Salkowski), but in some cases of slow poisoning the death has seemed to be ultimately caused by cardiac diastolic arrest. In Hoppe-Seyler's manometrical studies the arterial pressure was not affected until convulsions came on, when it rose from the effects of the general muscular contraction. It afterwards fell very decidedly and permanently.

Reduction of the arterial pressure has been shown by Gies to be the characteristic effect of the carbolic acid : in his experiments moderate

doses of the acid failed to affect the pressure after section of the cord, whilst in the normal animal neither asphyxia nor stimulation of a sensitive nerve elevated the lowered pressure, although the heart was beating forcibly,—facts that demonstrate that carbolic acid *paralyzes the vasomotor centre* in the medulla before it markedly affects the heart.

Respiration.—According to Salkowski, Labée, and other authorities, in the first stages of carbolic acid poisoning the respiration is remarkably increased in frequency. This acceleration Salkowski believes to be due partly to a stimulant action upon the peripheral vagi and partly to a similar influence upon the respiratory centres.

Salkowski states that the respirations are very shallow, and that the diaphragm scarcely participates at all in them, but that if the cervical vagi be cut they become much slower, deep, and regular. On the other hand, if carbolic acid be given to an animal suffering from section of the pneumogastrics, the slow breathing is very much accelerated. From the former of these facts the German investigator draws the conclusion that the accelerated breathing produced by phenylic alcohol is in part due to a stimulation of the peripheral vagi, and from the latter fact that it partly arises from a similar action upon the respiratory centres.

The final paralysis of respiration by carbolic acid is almost certainly due to a direct action upon the respiratory centres.

Temperature.—According to the researches of Hobart A. Hare,[32] carbolic acid injected into rabbits produces a very distinct fall in the bodily temperature, which is usually, but not always, coincident with the lowering of the arterial pressure. In the calorimetric studies made by Hare the effect upon heat-production and heat-dissipation in the normal animal appeared to be various, sometimes production and sometimes dissipation being alone affected, while in other cases both functions were altered. Some years ago Emil Erls[33] found that in mild putrid poisoning in animals carbolic acid diminished greatly the fever-heat; when the poisoning was more severe it had no influence. The calorimetric studies made by Hare upon fevered animals were fairly constant in their results, although the method of experimentation was not satisfactory, because the acid was given to the fevered animals at a time when it was uncertain what would have been the production of heat without its influences. Nevertheless, the experiments indicate that carbolic acid may affect the thermogenetic functions of the body in two ways: first, by diminishing the production of heat; secondly, by increasing the dissipation of heat.

Effects upon Tissues.—Post-mortem examinations of animals killed by carbolic acid have yielded varying results. In Lemaire's investigation, nothing abnormal was found except intense injection of the alimentary mucous membrane, a pseudo-membranous and purulent inflammation of the bronchial tubes, with a disseminated lobular pneumonia or else congestion of the lungs and of the nerve-centres. Bruckmüller, in Neumann's investigation, found the cells of the liver and kidneys in a state

of fatty degeneration. This process, which seemingly was the counterpart of the changes in phosphorus-poisoning, was always more advanced in the kidneys than in the liver. Neumann states that it was always present in his numerous autopsies, and that it is a constant phenomenon; but Salkowski was unable to find it in a number of examinations. In man the post-mortem appearances are very much the same as in animals. If the acid has been ingested in a concentrated form, white, hardened spots are found upon the mucous membrane of the mouth, œsophagus, stomach, and even intestines. They are, of course, due to the local action of the poison, and are sometimes blackish in the centre, or even blackish throughout, and very generally are surrounded by a red inflammatory zone. The liver, spleen, kidneys, and indeed all the organs, are found filled with dark, imperfectly coagulated blood, such as is habitually found after death from asphyxia. According to Husemann, the fatty degeneration of the liver and kidneys is neither in man nor in animals a constant or characteristic phenomenon of carbolic acid poisoning. Reuder[34] found the renal epithelium degenerated in a man who had been fatally poisoned by the drug.

THERAPEUTICS.—In the doses in which it is usually given, carbolic acid exerts no perceptible effect upon the system. It has been used to a considerable extent in zymotic diseases for the purpose of destroying the germs in the blood, but is of no value for such purpose. There is no reason for believing that micrococci or bacteria are more sensitive to its action than is the human organism; and clinical experience in these diseases has certainly demonstrated the uselessness of the acid. Our physiological knowledge conforms with clinical experience in showing that carbolic acid is of no value in constitutional diseases, and it is employed directly in medicine only for its local effects.

Internally, carbolic acid is a very valuable remedy in the treatment of various forms of nervous irritability of the gastro-intestinal mucous membranes, especially when there is also a tendency to fermentative changes in the food, as the result of imperfect digestion. In *nervous vomiting*, and in *gastrodynia*, it may be given in doses of from one to two grains, repeated at intervals varying from fifteen minutes to two hours, according to the symptoms of the case. In *diarrhœa* of *irritation*, as well as of *relaxation*, it is often of the greatest service. The combination of one or two grains of carbolic acid with ten to twenty grains of bismuth, given in emulsion or in capsules, is one of the most generally useful of diarrhœa mixtures.* In *gangrene of the lungs* the internal administration of carbolic acid combined with the use of a weak solution, ten drops to the ounce, by atomization, is said to be of great service. The use of carbolic acid as an antipyretic, as inaugurated by H. M. Desplats,[35] has not found favor, and is scarcely justifiable.

* In dispensing this, if capsules be used, the two ingredients should be thoroughly mixed before putting in: if an emulsion be employed, the bottle should be stood on its cork or laid upon its side, to prevent permanent separation of the bismuth.

The use of carbolic acid in *tetanus*, as originally proposed by Baccelli, has in a number of cases been attended by apparently beneficial results. Ascoli[36] has collected thirty-four cases with only one death. Exactly how it acts is not determined;. Heddaeus[37] believes that it neutralizes the toxin in the same manner as does the antitoxin. It is to be given hypodermically in the form of two per cent. solution, from five to fifteen grains (0.3–1 Gm.) in the twenty-four hours. (See H. C. Wood, Jr.[38])

The external use of carbolic acid belongs to the domain of surgery rather than of medicine, and we shall discuss it very briefly. As a *caustic*, carbolic acid is not available when large masses of tissue are to be destroyed, but it may often be employed with advantage against *condylomata* and similar growths. Even in such cases, to be efficient, it must be in the most concentrated form. In *diphtheria*, *ulcerated sore throat*, and *aphthous stomatitis* its concentrated solution in glycerin may carefully be applied, by means of a camel's-hair brush or a mop, as a mild caustic scarcely capable of destroying sound tissue. In various forms of *indolent ulcer* and in *ill-conditioned wounds* carbolic acid affords a very useful stimulant application; in *burns*, properly diluted with oil (ten drops to one fluidounce), it is one of the very best remedies that can be used, relieving pain by its anæsthetic properties and at the same time lessening suppuration and facilitating cicatrization.

The use of carbolic acid as a local anæsthetic has been entirely done away with by the discovery of the powers of cocaine.

So far as we know, the first to suggest and employ *deep injections* of carbolic acid as a means of combating *deep-seated inflammations* was J. A. Eames;[39] but the method has been especially studied by C. Hueter.[40]

Hueter employs a two per cent. solution, a weaker one not being efficient and a stronger one endangering the coagulation of the blood and of the exudation in the inflamed tissue. Of this solution he uses at one time never more than half a drachm, and generally less than this. After anæsthetizing the skin by the local application of carbolic acid, he introduces the hollow needle into the centre of the inflammation obliquely, so as to diminish as far as possible the chances of the introduction of air. To avoid the danger of throwing the acid directly into the circulation, the needle is not connected with the syringe until it is seen that no blood comes out through it. If the extent of inflamed tissue be large, several injections are practised at one time: in acute cases they are usually repeated twice a day, in chronic cases every day or every other day. Hueter has made about a thousand of these "parenchymatous injections," and only ten times has any inflammation been excited by them. The pain is usually very slight, and the relief apparent in one or two days at most.

In *chronic synovitis* carbolic acid may be thrown into the joint once in two or three days, and the method has been practised by Hueter with asserted extraordinary success in *glandular swellings and inflammations*, *phlegmons* of all grades and characters, *erysipelas*, *poisoned wounds*, *inflamed bursæ*, *hydrocele*, and even in *bone disease*.

The practice has been followed with satisfaction by Aufrecht[41] in *ery-*

sipelas, by Senator,[42] Mader,[43] and Kunze[44] in acute and subacute *rheumatism*, by Hagen[45] in several diverse inflammations, and by I. Schmidt[46] in chronic *synovitis*. Hagen has even used these injections with very excellent results in three cases of severe *angina* which he believed threatened diphtheria, throwing the remedy into the neighborhood of the second tracheal cartilage. Moses K. Taylor[47] has used injections in one hundred and fifty cases of *buboes* and other enlarged glands, with uniform success. The total evidence seems to show that this method of treatment is both safe and effective.

TOXICOLOGY.—Probably on account of the ease with which it is procured and the quickness of its action, carbolic acid is among the most popular of poisons. According to Harris,[48] out of five hundred and forty-nine fatal cases of poisoning which occurred in England during four years four hundred and twenty were suicidal.

The symptoms usually appear in a very short time after the ingestion of the poison, and when the dose has been sufficient may develop so rapidly that death occurs within three minutes. Usually the patient lives from one to ten hours, and life has been protracted for sixty hours.*

Taylor[49] records a case in which about an ounce is supposed to have been ingested, and in which the man fell in a stupor within ten seconds after taking the fatal draught, two minutes afterwards was totally unconscious, pulseless, with irregular distant gasping respirations, and in less than a minute later was dead, apparently from cardiac paralysis, since the impulse of the heart was entirely lost before the cessation of respiration.

Usually, but not always, a burning pain is first felt in the mouth, œsophagus, and stomach, followed in a few minutes by nausea, cold sweats,† and stupor deepening rapidly into insensibility and collapse. During the period of insensibility, complete abolition of reflex movements and anæsthesia of the mucous membranes have sometimes been noted :‡ indeed, it is scarcely doubtful that in all cases both sensibility and reflex movements are profoundly affected. Convulsions are only exceptionally present. The symptoms of collapse are usually well developed, and the pulse is generally feeble and very frequent, but has been recorded as being reduced to from 40 to 50 per minute.§ Hæmoglobinuria has been noted. Dyspnœa is often extreme ; the respirations may be stertorous, are usually very rapid, and, in the advanced stages, shallow. In very rapid cases they are irregular and suspended

* Case, *Sydenham Soc. Year-Book*, 1871–72, 446; amount taken, one and a half ounces of the commercial acid.

† The excessive sweating sometimes seen in carbolic acid poisoning Th. Gies believes to be of central origin, since in a poisoned cat with one sciatic nerve cut no sweat came from the injured part.

‡ Case, *Journ. de Pharm. et de Chim.*, Dec. 1871.

§ Case, *Med. Times and Gaz.*, April, 1871.

at intervals. Total temporary amaurosis, with contraction of the pupil, has been noted.*

In some cases of carbolic acid poisoning a great amendment has occurred and consciousness been restored, but after some hours rather sudden fatal collapse has come on.† The minimum fatal dose of carbolic acid is not known; but half an ounce has several times caused death,‡ and a little over a drachm is reported to have killed a man sixty-four years old;[50] in a case of puerperal metro-peritonitis fifty drops contributed towards the fatal result (A. D. L. Napier[51]).

The free external use of carbolic acid is by no means devoid of danger; Falckson,[52] after two hours' exposure to carbolic acid spray, recovered from his urine thirty grains of carbolic acid, and he describes a marasmus or chronic poisoning resulting from the surgical use of the remedy. The symptoms are said to be headache, loss of appetite, bronchial irritation, which finally may become very severe, severe pains in the region of the kidney, recurring vomiting, pruritus, or various paræsthesiæ, and loss of power in the legs. (See also Wallace.[53])

A single vaginal injection has produced very severe constitutional results.[54] R. Köhler[55] reports the cases of two journeymen joiners, suffering from scabies, who applied externally each about a half-ounce of carbolic acid, in watery solution. One of them was found dead. His fellow, who suffered from unconsciousness and drunken delirium ending in unquiet sleep, after his recovery stated that directly after rubbing himself with the solution he had giddiness, that seven or eight minutes later his companion complained of burning, but that of what took place after this he knew nothing.§

It is scarcely necessary to refer in detail to cases in which serious results have followed the surgical use of carbolic acid.‖ A very severe case of poisoning is recorded, in an infant,[56] produced by the use of carbolized cotton wool. The local application of carbolic acid has in a number of instances been followed by local gangrene,¶ which A. Frankenburger[57] has determined to be the result of thrombosis.

The diagnosis of carbolic acid poisoning during life ought in most cases to be practicable; for, although the symptoms simulate some forms of apoplexy too closely for the diagnosis to be made from them, very generally the odor of the drug can be perceived about the person of the victim, and close examination of the mouth will nearly always reveal

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* Case, *Berlin. Klin. Wochenschr.*, xix. 748.

† Case, *Brit. Med. Journ.*, Feb. 1861.

‡ *Med Times and Gazette*, 1870, ii. 474; *Phila. Med. and Surg. Rep.*, Jan. 1870; *Lancet*, 1878, ii. 510.

§ For other fatal cases, consult *Bull. Thérap.*, lxxv. 285.

‖ Consult *British Medical Journal*, March 1, 1873,—death from absorption by a wound four inches long; *New York Medical Gazette*, April, 1871; *British Medical Journal*, 1868, 220,—two fatal cases; *Med. Times and Gaz.*, 1878, ii. 461; *Wiener Med. Wochenschrift*, 1879, xxix. 1233.

¶ For cases, see *Med. Times and Gazette* 1870, ii.; *L'Abeille Méd.*, 1871; *Med. News*, 1890, i.; *Bull. Soc. Méd. d. Hôp. d. Paris*, 1889, vi.; *Schmidt's Jahrb.*, cclvii. 197.

traces of the local action of the acid, in the form of *white, hardened*, or *corrugated* patches of mucous membrane. Either these or a *blackish urine* in conjunction with the symptoms are diagnostic. After death a strong odor of carbolic acid can almost always be perceived when the body is opened, and the mucous membrane of the stomach affords very reliable evidence as to the cause of death. According to A. Hiller, the urine of carbolic acid poisoning as first passed varies from a clear yellow to a golden yellow, and upon standing in the air becomes dark olive and finally often blackish green. Sometimes it is grass-green, but it may appear to be normal.[58] This carbolic acid urine, if treated with nitric acid and afterwards with potassa, becomes, after a certain degree of concentration, blood-red or brown-red, changing through pea-green to violet. Carbolic acid mixed with urine does not answer this test.[59]* The absence of carbolic acid urine proves that the case is not one of poisoning. Baumann and Hueter[60] declare that the earliest symptom of the poisoning is disappearance of the sulphates from the urine.†

In a case of carbolic acid poisoning emetics are generally useless, owing to the existing paralysis of the stomach, and the stomach-pump must be employed to empty the viscus. As the antidote of carbolic acid, alkalies in excess have been especially commended by Husemann, who employs the saccharate of lime;‡ whilst formerly the free ingestion of oils was strongly urged by authorities. In 1878 Baumann and Hueter[61] stated that if a dilute sulphuric acid or a soluble sulphate be given freely to the animal poisoned with carbolic acid the latter will be converted into a harmless sulphocarbolic acid.§ Subsequently Sonnenburg affirmed that in patients suffering from the too free external use of the acid all symptoms disappear upon the administration of sodium sulphate, and it at that time appeared to be established that the innocuous soluble sulphates have the power not only of rendering carbolic acid in the alimentary canal innocuous, but also of following it into the blood, and there converting it into a harmless sulphocarbolic acid.

The present evidence regarding the antidotal value of the sulphates in carbolic acid poisoning is, however, not entirely clear. David Cerna,[62] in an elaborate series of experiments upon animals, employed the magnesium sulphate with entire success. Cafrawy[63] reached experimental results similar to those of Cerna. S. Tauber,[64] however, challenged the correctness of this, affirming that the doses used

* For method of detecting carbolic acid in urine, see *Lond. Med. Rec.*, 1877, 455.

† To detect the diminution of sulphates in the urine, remove any albumin present by boiling, acidify with acetic acid, and add barium chloride in excess. This reagent gives a milky cloud of barium sulphate in the presence of sulphates, but a mere haze or no alteration in carbolic acid poisoning.

‡ Dissolve sixteen parts of sugar in forty parts of distilled water, and add five parts of caustic lime; digest for three days, stirring from time to time, filter, and evaporate to dryness. The product thus obtained dissolves easily in water.

§ For a study of sulphocarbolic acid, see *La Tribune Méd.*, July, 1884, 328. M. F. Vigier affirms that, while not poisonous to the higher animals, it is an active antiferment. M. Rabuteau (*Compt.-Rend. Soc. Biol.*, 1882, iii. 42) finds that the acid is simply a feeble purgative.

by Cerna were not really lethal, and giving a number of experiments in which neither the sodium sulphate nor the pyrosulphate evinced any antidotal influence in the poisoned rabbits. He further concluded, as the result of his experiments, that the sodium sulphite is of distinctly antidotal value.* On the other hand, Jos. Szydlowsky[65] saved a pulseless and apparently dying child, ten hours after the ingestion of the carbolic acid, by hypodermic injections of ether and the administration of dilute sulphuric acid and sodium sulphate. In the present state of evidence the practitioner must remain in doubt as to the proper antidote for carbolic acid, but in our opinion a trial of a soluble sulphate should be made, though a sulphite and olive or linseed oil may also be exhibited.

The best conclusion that can be formed from the present evidence is that which was reached in 1894 by Pio Marfori[66] as the result of his own experiments,—namely, that the soluble sulphates, given either through the gastro-intestinal canal or injected hypodermically, are distinctly antidotal to carbolic acid, but that there is a limitation to their power, so that if too much of the phenol has been taken the sulphates will prove of no practical value. Alcohol has been strongly recommended as an antidote by Phelps,[67] Fraser,[68] and others.

CREOSOTUM. U. S.—CREOSOTE—CREASOTE.

This substance is defined by the U. S. Pharmacopœia to be a mixture of phenols, chiefly guaiacol and creosol, obtained during the distillation of wood-tar, preferably of that derived from the beech (*Fagus sylvatica*, Linné). The creosote of commerce is an oleaginous liquid, colorless, or brownish or reddish, having a caustic taste and a penetrating disagreeable odor, which whilst resembling that of carbolic acid markedly differs from it in being more smoky. It is neither acid nor alkaline in reaction, and forms in water two solutions, having respectively the strength of one to ten and one to eighty. As it occurs in commerce it varies in constitution; and, indeed, even creosote conforming to the official tests varies in the proportion of its ingredients. It consists chiefly of guaiacol and creosol, though certainly other phenoloid bodies occur in it. It is stated that the beech-wood creosote varies in the amount of guaiacol from sixty to ninety per cent. It has been much confused with carbolic acid, and for many years most of the creosote of the drug-stores was an impure carbolic acid. For the tests distinguishing creosote from carbolic acid, see United States Dispensatory.

Physiological Action.—The physiological effects of creosote have never been carefully and thoroughly studied. It certainly rivals carbolic acid in its antiseptic power. It is, when applied locally, a paralyzant to the nerves, and probably to all higher tissues; indeed, it has been generally believed to be almost identical in the range and powers of its activity with carbolic acid. It differs, however, greatly from

* De la Bate (*Bull. Gén. de Thérap.*, cv. 418) affirms that he obtained very happy results in one case of carbolic acid poisoning from inhalations of oxygen.

carbolic acid in its toxicity, as well as in the ra
disease.

Freudenthal[1] reports the case of a woman who t
creosote in a very short time, the ingestion being follo
unconsciousness, with intense trismus, contracted imn
cyanosis, but in which recovery occurred without the a
He further states that subsequently this same patient,
creosote, was able to take five hundred drops daily with

The symptoms have been similar to those c
ing,—namely, burning in the gullet and stomach
consciousness, collapse, blackish urine, stertorou
cardiac depression. Zawadzki[2] reports a death
produced by three six-drop doses of creosote, t
hours.

The absorption and elimination of creosote a
within the nine hours following the administration
obtained from the urine forty-eight milligramm
grammes, one hundred and eleven milligramme
that about two-thirds of the dose escapes from
kidneys in the time mentioned. Imbert[4] recover
acol from the urine after the hypodermic injec
after two grammes of a mixture of guaiacol a
grammes; and so on: so that it would appear th
sote is destroyed in the body. This conclusio
doubtful by the fact that the creosote escapes thro
the kidneys. It has been found abundant in
patients, and, indeed, Catillon[5] affirms that i
through the lungs. It occurs in the urine prob
educts, but chiefly as creosol and guaiacol sulph
by Hobert A. Hare,[6] sulphuric acid and the sol
dotal to it.†

THERAPEUTICS.—Creosote has been used i
germicide; second, for its local effects. On a
influence on the tubercular bacillus it was introd

* For other cases of creosote-poisoning, see Müller (*Wü*
1869), T. Stevenson (*Guy's Hosp. Rep.*, 1875, xx. 144), Pürc
f. Gericht. Med., 1883, 430), F. Grinell (*Med. News*, xl.
Légale de France, vii. 108), and Faisans (*Bull. Méd. Soc. M*

† Imbert finds that the proportion of creosote eliminated
of the dose. Thus, after an enema of one gramme, fifty-fou
in the urine; after two grammes, forty-eight per cent.; after
When four grammes were administered, the expectorations s
hours. After a subcutaneous injection, Imbert was not able
more of the creosote than after it had been given by enema.
persistent pain and swelling, no suppuration or sloughing e
Imbert also found that the elimination ceased at the end
well as small doses (*Bull. Gén. Thérap.*, 1892, cxxii.). For
the urine, see also *Bull. Gén. Thérap.*, May, 1892.

phthisis. It has received in this disease much commendation, especially from Sommerbrodt, who has reported thirteen years' experience with it. He insists on the necessity of the purity of the creosote, and of the use of large doses—one to two grammes per day—for many months or years. Our own experience is in accord with the general drift of the clinical results obtained by authors, in showing that whilst creosote is a valuable remedy in phthisis, it is not a specific, and will rarely, if ever, bring about a cure : that it acts in these cases by poisoning the bacilli is very doubtful. Any such action must be purely local,—*i.e.*, due to creosote excreted in the lung,—since F. Hölscher and Richard Seifert[7] found that in young rabbits and dogs to which guaiacol had been freely given the serum of the blood was at no time capable of checking the development of bacilli in agar-agar : the conclusion of the experimenters just named, that guaiacol during absorption becomes converted into an albuminous compound which has no influence upon the lower organisms, is plausible. It seems to be established that creosote is largely eliminated with the sputa ; but Bogdonovitch and other clinicians or experimenters have found the bacilli abundant and active in the sputa of phthisical persons taking the remedy. Brissonet[8] and Hölscher and Seifert present evidence to show that guaiacol neutralizes in the blood those poisonous products of bacillary growth which are the cause of the fever, sweating, disordered digestion, etc., of the phthisical patient ; in other words, that creosote acts chemically in the blood. At present this seems to be nothing more than an ingenious theory. In our experience, creosote acts most favorably in cases with very free expectoration, and we have seen it do so much good in simple pulmonary catarrh not resting upon a tubercular basis, that we believe it to be simply a valuable alterative, stimulant expectorant, which also may do good by checking intestinal fermentation and improving the digestion.

On account of its local action as a nerve paralyzant, creosote is frequently employed with great advantage in *nausea*, *vomiting*, or *diarrhœa* dependent upon excessive irritability, without acute inflammation, of the gastric or intestinal mucous membrane ; it has thus been successfully used in the *vomiting of pregnancy* or of *hysteria*, in *cholera morbus*, *cholera infantum*, *lienteric diarrhœa*, *typhoid fever*, and even in *dysentery*. When in these cases there is a tendency to fermentation of the contents of the stomach or bowels, creosote is especially valuable, and may often be combined advantageously with an alkali or chalk. Whether it is in these affections superior to carbolic acid is doubtful.

Externally, creosote has been employed for exactly the same purposes as has carbolic acid. The skin diseases to the treatment of which creosote has been supposed to be best suited are those of a scaly character. In *burns* its efficacy has been insisted on, especially when there is excess of suppuration or of fungous granulations. In *chilblains* also it is stated to be a useful application. Mixed with four parts of lard, it is said to have proved very serviceable in *erysipelas*. When applied to wounds it

acts as a hæmostatic, stopping the capillary hemorrhage, but it possesses no power to arrest the bleeding from large vessels. Accordingly, creosote water has been applied locally in *menorrhagia*, and to arrest *uterine hemorrhage* and the bleeding from leech-bites. Wherever there are *foul ulcers*, gangrenous surfaces, or inflamed serous, mucous, or glandular tissues giving rise to fetid discharges, creosote may be substituted for carbolic acid; as examples may be mentioned fetid *leucorrhœa*, puerperal *metritis*, fetid *otorrhœa*, putrid or *diphtheritic sore throat*, chronic *empyema*, and chronic *fistula*. The strength of the application may vary from that of pure creosote to a single drop to the fluidounce of water, according to the delicacy of the part and the severity of the disease.

Numerous attempts have been made to bring creosote in direct contact with the tuberculous lung. Thus, its solution in oil has been by various practitioners injected directly into the pulmonary parenchyma.[1] Dor's method consisted of injecting into the trachea from five-tenths to two centimetres of the five per cent. solution of creosote in olive oil previously boiled. Neither theory nor result seems, however, to justify these violent procedures. The inhalations of the vapor of creosote have been very largely used by means of respirateurs or other mechanical contrivances, and the British Pharmacopœia recognizes VAPOR CREOSOTI (twelve minims to eight fluidounces of boiling water).

The ordinary dose of creosote is from three to five minims (0.12–0.3 C.c.) three to six times a day, in chronic cases increased to one or even two fluidounces a day, as borne by the patient. Creosote in capsules should be taken upon a full stomach. Large doses of it should always be administered dissolved in a considerable bulk of water and glycerin, or of spirit and water, or of cod-liver or other oils, so as to avoid local irritation. Creosote has also been used hypodermically in phthisis. Thus, Perom employed a ten per cent. solution in oil of sweet almonds, two injections of eighty minims each being given daily. This method of administration does not seem, however, to present sufficient advantage to counterbalance the pain and local irritation caused. Dose of creosote water (AQUA CREOSOTI—one per cent., U. S.), half to one fluidrachm (2–4 C.c.).

CREOSOTUM CARBONICUM. — *Creosote Carbonate.* — *Creosotal.* — A mixture of the phenol-carbonates of the several constituents of creosote, containing about ninety per cent. of pure creosote. It is a thick, oleaginous, pale yellow, almost tasteless liquid, insoluble in water, soluble in fatty substances. It has been highly recommended, especially by Leyden, as a substitute for pure creosote in *phthisis*, *bronchitis*, and other pulmonic diseases, as having the advantages of being less disagreeable to the taste and better tolerated by the digestive apparatus. It is decomposed in the system, and is capable of producing blackish urine. It is, however, much less poisonous than is creosote, and probably when large doses are exhibited escapes in part from the alimentary canal. Fifteen drachms

of it are asserted to have been given in a day without unpleasant symptoms ; and it has been used hypodermically after warming, so as to increase its fluidity. It may be given in capsules, or preferably in emulsion in milk. Ordinary dose, five to ten grains (0.3–0.6 Gm.), administered three to six times a day.

GUAIACOL (*Methyl Pyrocatechin*) is a phenoloid body which constitutes from sixty to ninety per cent. of creosote. When chemically pure it is a syrup-like liquid, of an agreeable odor and taste, which yields under chemical manipulation various derivatives that have been employed to some extent in medicine. The general physiological action of guaiacol and its derivatives has not been studied to any extent, but is probably similar to that of creosote. According to the researches of André, which have been confirmed by various surgeons, the substance has distinct anæsthetic powers, which do not, however, seem to be sufficient to render it suitable for use as a local anæsthetic, though they may increase its value as a local application in various surgical disorders.

As a germicide, according to the experiments of J. Kuprianow,[1] guaiacol is much inferior to creosote and to carbolic acid, in that it is necessary for it to be present in comparatively large proportion. On the other hand, it seemed in the experiments just spoken of to be especially poisonous to the tubercle bacillus. It has been highly recommended by Max Schueller, of Berlin, as a valuable local remedy in *lupus* and other forms of external and surgical tuberculosis, and is used to a considerable extent by surgeons for such purposes. It has been strongly recommended in *tuberculosis of the bladder*, and even in an ordinary *chronic cystitis*. From fifteen to thirty minims of the solution made with sterilized olive oil (five per cent., increased to twenty per cent. if necessary) may be injected into the bladder once or twice a day. Very frequently, it is alleged, one per cent. of iodoform may be added to this solution with great advantage.

Guaiacol is absorbed and eliminated with the greatest rapidity. Linossier and Lannois[2] were able to recognize it in urine passed fifteen minutes after its local application to the skin, and to obtain from the urine of the next twenty-four hours nearly half of the whole amount used. In the experiments of Eschle[3] the greatest part of the ingested guaiacol or guaiacol carbonate was eliminated within twenty-four hours, about half of it going out with the urine in combination with sulphuric acid ; of the remainder the greater part was eliminated as glycuronic acid.

Max Schueller at one time strongly commended the general use of inhalations of the aqueous solution (1 to 600) in *phthisis*, but more recently teaches that the inhalations should be confined to cases in which there is distinct catarrh of the respiratory mucous membranes. The suggestion of Guinard[4] that guaiacol be used externally as an antipyretic in phthisis has led to its trial in *pneumonia*, *typhoid fever*, and other acute diseases. The thoroughly cleansed skin of the abdomen or chest is

painted by means of a camel's-hair brush with from twenty to fifty minims, and an impermeable dressing applied to prevent evaporation. The fall of temperature produced by the guaiacol used in the manner described follows with great certainty, but has too often been excessive and accompanied by pronounced collapse to allow the drug to be considered a practical antipyretic.

GUAIACOL COMPOUNDS.—A number of compounds of guaiacol have been put upon the market, the most important probably being *guaiacol carbonate* or *duotal*, a neutral white crystalline powder with very feeble odor and taste, insoluble in water.

The dose of guaiacol carbonate is commonly set down as from five to ten grains (0.3–0.6 Gm.), but it is probable that very much larger amounts may be given without danger, as it has been shown that in the lower animals guaiacol carbonate is much less poisonous than guaiacol. (See W. Hesse.[5]) Indeed, so slightly toxic is this carbonate that it seems to us probable that much of it escapes from the alimentary canal unabsorbed.

MENTHOL, U. S., or *Oil of Peppermint Camphor*, has obtained great notoriety as a local anæsthetic, and, if freely rubbed upon a part, it undoubtedly will often relieve neuralgic pains when they are superficial and peripheral in their origin: its solution (2 to 10 grs.—f℥i water) is said also to be very effective in *pruritus ani*, *chronic painful eczemas*, *urticaria*, etc. Its physiological action has been studied by Paolo Pellacani.[1] In the frog it causes paralysis, first of the spinal centres and finally of the nerve-trunks. In the mammal both mobility and sensibility are depressed, the animal grows cold, and the respiration becomes slow and shallow. Small doses excite, larger paralyze the frog's heart. In the poisoned mammal there were very curious, unexplained rhythms of rise and fall of the blood-pressure.

Goldscheider[2] has been led to the conclusion that the sensation of cold produced by the local application of menthol is due to a special influence exerted upon the special nerves of temperature by finding,—first, that after the application of a solution of menthol in lanolin the local temperature is increased 2° C., although a marked sensation of cold has been produced; and, secondly, that the cold is not due to evaporation, because covering the part to which the menthol is applied with a watch-glass does not affect the sensation. He also found that if the menthol ointment were applied to one side of the forehead, bodies which previously had caused the sensation of cold no longer did so, and that applications of menthol produced a sensation of warmth upon the elbow and the volar side of the wrist, positions at which, according to Herzen, similar warm sensations are caused by pressure upon the nerve-trunks.

S. A. Russell[3] affirms that menthol has a remarkable power of controlling superficial inflammations. He applies an ethereal solution, of the strength of from ten to fifty per cent., two or three times a day by

means of a camel's-hair pencil, and asserts that he is able to control thereby *boils*, *carbuncles*, *superficial abscesses*, etc.*

THYMOL. U. S.

Thymol is found in the oil of thyme † and of some other plants. It occurs either as an uncrystallizable liquid or in white rhombic or acicular crystals. It has been used with satisfaction as a substitute for carbolic acid by Volkmann and Ranke, of Halle, and other practitioners, but, although it is undoubtedly powerfully antiseptic, does not seem to have gained favor. Its fragrant odor has proved a decided disadvantage, in summer at least, by attracting swarms of flies. It is not free from poisonous properties. It is asserted that it does not irritate the skin, and has a decided influence in preventing discharges. Spencer Wells employs its watery solution (1 to 1000 of warm water); Volkmann, thymol one part, glycerin twenty parts, alcohol ten parts, water one thousand parts. It has been used internally by Bälz[1] in doses of thirty grains a day, or less. In a few instances nausea and vomiting were caused. There were abundant sweating, singing in the ears, deafness, constriction in the forehead, reduction of temperature, and frequently diarrhœa. The urine was dark greenish, yellowish brown by transmitted light, free from albumin, becoming cloudy and grayish white on the addition of the tincture of the chloride of iron. Violent delirium occurred several times, also marked collapse, and, in one case of typhoid fever, unconsciousness, with most alarming collapse. Bälz concludes that the remedy is much less certain and more dangerous as an antipyretic than is salicylic acid.

The possession of poisonous properties by thymol has been confirmed by the recent experiments of B. Küssner.[2] This observer found that when given to dogs and rabbits by the stomach the poison acts very slowly and feebly, on account of its slow absorption, but when injected into the circulation it produces death by failure of respiration. Coma is developed some time before death, and the blood-pressure, which at first maintains itself, falls steadily. Post-mortem examination failed to detect fatty degeneration or other lesion in either the solid tissues or the blood. The continuous repeated exhibition of small doses of thymol had no perceptible effect, except to interfere in some way with nutrition, so that the animals lost flesh.

Küssner has found that thymol has the power of dissolving the red blood-corpuscles.‡ Thymol is eliminated through the kidneys partly as

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**Camphor-Menthol.*—When equal quantities of pure menthol and camphor are triturated together a clear liquid is formed. It has been strongly recommended by S. R. Bishop (*Kansas City Med. Ex.*, 1892) as a local application in *rhinitis* and *laryngitis*, twenty per cent., and full strength in *eczema*.

† According to Cardeac and Meunier (*Journ. Med. Vet. Zootech.*, 1890), the physiological actions of the oils of *Thymus serpyllum* and of *Thymus vulgaris* are the same; they produce in animals dilated pupils, staggering gait, hallucinations, loss of sensibility, muscular relaxation, insomnia, trembling, contractures, exceedingly rapid respiration, and death, preceded by complete muscular relaxation and anæsthesia.

‡ See *Hoffmann und Schwalbe's Jahresb.*, 1879, 208.

thymol itself, partly as thymo-hydrochinone united with sulphuric acid, partly as a chromogen, which is probably an oxidation product of thymol, and partly as some acid of unknown constitution (F. Blum[3]).

Thymol is, on the whole, inferior to other drugs of its class for either internal or external use, but on account of its agreeable taste is often preferred as a detergent antiseptic in various ulcerated and diseased conditions of the mouth. The value ascribed to the drug in *diabetes* by Küssner has not been sustained;* nor has it come into vogue as an intestinal antiseptic in *typhoid fever*, for which purpose it was highly commended by Martime and by F. P. Henry.[4] Dose, fifteen to twenty grains (1–1.3 Gm.) in the twenty-four hours.

Thymacetin is a white crystalline powder, very slightly soluble in water, which has the same chemical relation to thymol that phenacetin has to phenol. According to Solly,[5] it is a valuable analgesic in neurotic pains and is also soporific. Dose, five to fifteen grains (0.3–1 Gm.), in capsule.

RESORCINUM—RESORCIN.† U.S.

Resorcin, *pyrocatechin*, and *hydroquinone*, three dioxybenzols, resemble each other very closely in physiological effects, but of them only resorcin is used in medicine. It occurs in colorless, short, aromatic prisms or plates of an unpleasantly sweet, somewhat acrid taste, which on exposure to the air become reddish. It is freely soluble, at 59° F., in 0.6 part of water, in alcohol, in ether, and in about twenty parts of fixed oil.

PHYSIOLOGICAL ACTION.—*Local Action.*—*Elimination.*—Resorcin is an active irritant, but is scarcely able to act as an escharotic. According to Joseph Schomacker,[1] it is eliminated with the urine as a sulpho-acid, which on boiling with HCl is decomposed, resorcin being set free; after very large doses, free resorcin may be found in the urine. The excretion is said to be completed in about seven hours. It is actively poisonous to the lower organisms, and, according to Martin Cohn[2] and Andeer,[3] a one per cent. solution of it is sufficient to arrest for a long time putrefactive changes in the urine, organic infusions, and even animal tissues. Platt[4] states, however, that it is distinctly inferior to carbolic acid as an antiseptic.

General Effects.—In doses of twenty to forty grains resorcin causes flushing of the face, with giddiness, buzzing in the ears, and some quickening of the breathing and pulse, followed, after a time, by violent perspiration and sometimes depression of temperature. Sixty grains caused in man giddiness and violent perspiration, with marked anxiety, ending in collapse and unconsciousness.

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*See Fürbringer (*Deutsches Archiv f. Klin. Med.*, xxi.)

† *Thioresorcin* is a sulphur substitution-product from resorcin. A case of poisoning by its external use is reported by H. Amon (*Münch. Med. Wochenschr.*, 1889, xxxvi.). The most peculiar symptom was erythematous œdema of the face, and general eruption somewhat similar to that of measles, with intense itching.

Andeer took about one hundred and fifty grains of resorcin, dissolved in a pint of water, during fifteen minutes. After disturbance of the cerebration and of the special senses, he fell into a condition of collapse, with cold extremities, epileptiform convulsions with loss of consciousness, opisthotonos, and marked disturbance of the respiration. Consciousness did not return for five hours. Murrell[5] records a case in which a woman took one hundred and twenty grains of resorcin, and immediately felt giddy, had sensation of pins and needles all over her, and a few minutes later was insensible, with closed eyes, clinched hands, pallid, blanched lips, dry tongue, normal pupils, and insensible conjunctiva; the temperature was 94° F.; the reflexes were entirely gone; the pulse was weak and thready. Jos. Loeffler[6] reports the case of a woman, thirty-one years old, who, immediately after the injection into the stomach of two litres of a three per cent. solution of resorcin, was seized with violent gastric pain, followed at once by unconsciousness, cyanotic face, and clonic contractions. In spite of the immediate removal, as far as possible, of the solution, the cyanosis became more intense, the unconsciousness and muscular relaxation complete, with, from time to time, active tremors; the pulse very small and frequent; the respiration completely arrested, with respiratory muscles in such a condition of tetanus as greatly to embarrass artificial respiration. Under the continued use of artificial respiration, however, recovery was finally secured. In several cases of children the washing out of the stomach with a three per cent. solution has been followed by collapse and death, and in one case hæmoglobin was found in the urine.

In the lower animals (Dujardin-Beaumetz[7]) resorcin causes tremors, loss of consciousness, and epileptiform convulsions, which, when the dose has been sufficiently large, become more and more violent, until the increasing disturbance of breathing ends in respiratory arrest. During the spasms the temperature of the animal is distinctly elevated, but when there is quiet narcosis it may fall below normal. The urine becomes olive-green, deepening into blackish.

Resorcin resembles carbolic acid in being a universal poison, but is less active. It probably affects the nerve-centres as does carbolic acid, and has been shown by Beyer to have a direct paralyzant effect upon the heart.

THERAPEUTICS.—On account of its being less efficient and more dangerous than other members of its class, resorcin is used solely as a valuable topical remedy in diseases of the skin and mucous membranes. It has been highly recommended by Hoefer, Lichtheim, Janicke, Fliesburg, Baginsky,* and others in various acute and subacute gastric or intestinal inflammations, such as *enteritis*, *gastric ulcer*, and *cholera infantum*, but in our experience has not given satisfaction. In *hay fever*, *chronic otitis*, *gonorrhœa*, *leucorrhœa*, and other mucous catarrhs it may be applied locally in the solution of from one to fifteen per cent. The three to five per cent. solution has been largely used in Germany in washing out diseased stomachs, but care is necessary to avoid poisoning. In chronic *cystitis* irrigation of the bladder with a three per cent. solution has been found effective.

It is said to be valuable in the treatment of the various parasitic skin diseases such as *tinea* and *scabies*. Too irritating for acute inflammations of the skin, it certainly exerts a powerful effect on recent cell-infiltrations,

* See *Therap. Gaz.*, ii. and iii., and *Berliner Klinische Wochen.*, 1889, xxvi.

and is extraordinarily successful in chronic and subacute *eczema*, where there is much thickening from exudation, in *seborrhœa*, and even in *psoriasis* and *pityriasis*. It is preferably used in solution : from ten to thirty grains in one drachm of alcohol, one drachm of glycerin, and eight drachms of water, well sopped on the part and allowed to dry. According to Andeer, resorcin, in powder or in saturated ethereal solution, is a feeble caustic, useful in the treatment of *chancres*, of *papilloma*, and even of *epithelioma* and *diphtheria*. Dose, two to five grains (0.13–0.3 Gm.).

ACIDUM SALICYLICUM—SALICYLIC ACID. U.S.

Salicylic acid occurs in long acicular crystals or in the form of a white, dull powder, of a peculiar pungent odor, and a mild, peculiar taste, accompanied by a transient sense of numbness. It is soluble, at 59° F., in about four hundred and fifty parts of water and in 2.4 parts of alcohol.

PHYSIOLOGICAL ACTION.—*Local Action.*—Pure salicylic acid is actively irritant to mucous membranes. This is, however, hardly true of the salicylates, although it is notorious that these salts are very prone to produce indigestion, with loss of appetite, and even nausea. These symptoms may be in a measure connected with the exceedingly disagreeable taste of the drug, but it is probable that they are more largely due to a direct interference by the salicylates with the action of the digestive ferments upon the food.

According to Kolbe and others, salicylic acid arrests or prevents the action of the non-organized organic ferments. Thus, it will inhibit the action of emulsin upon amygdalin or upon myronic acid, and prevent the development of hydrocyanic acid or of the volatile oil of mustard. Miller found that one per cent. of salicylic acid was sufficient to check the action of ptyalin upon starch ; for the same effect ten per cent. of carbolic acid was required. The digestive action of pepsin, outside of the body, was very seriously affected by 0.2 per cent. of salicylic acid in Miller's studies, but in Kolbe's experiments the ingestion of twenty grains a day of the drug had no demonstrable effect.

Absorption and Elimination.—Salicylic acid appears to be absorbed very rapidly. Drasche[1] affirms that almost immediately after the application of its alcoholic solution to the sound skin, the acid may be found in the urine ; and in Kumagawa's experiments, salicylic acid was so rapidly absorbed from the intestines that it failed to diminish the indican of the urine by checking fermentation in the intestines.

Owing to the insolubility of salicylic acid, the problem of the method of its absorption and of the state in which it circulates in the blood early attracted attention. Salkowski[2] pointed out that the acid in the blood probably exists in the form of a sodium salicylate. Binz[3] supposes that the acid is liberated in the blood by the carbonic acid formed in the tissues. The only basis for this theory consists in the fact that by passing carbonic acid gas through a solution of sodium phosphate, carbonate, and salicylate, agitating with ether, and separating and evaporating the latter, crystals of salicylic acid are obtained. It is evident that if

in the blood changes take place similar to those which occur in this solution, salicylic acid should be yielded to ether shaken with the blood of an animal poisoned with the drug. Feser and Friedeberger found that unless enormous doses of the drug were injected into the blood, so as to produce immediate violent convulsions and death, the vital fluid of the poisoned animal yielded nothing to ether. In Köhler's[4] experiments, when salicylic acid was dissolved in normal blood no acid was yielded to ether, but when the blood of asphyxia—*i.e.*, blood supersaturated with carbonic acid—was employed, a very notable amount of the acid was extracted by the ether. These experiments warrant the conclusion that when the blood is in the normal condition the alkaline salicylates are not decomposed by the carbonic acid in it.

Feser and Friedeberger have advanced the theory that the salicylic acid circulates in the form of an albuminate. This has received some support from the experiments of Farsky,[5] which seem to show that the acid is capable of forming such a compound.* On the other hand, the theory is contradicted by the results of Fleischer,[6] who digested albuminous solutions with the acid, and after coagulation by heat found all the acid in the filtrate, and who also treated the blood of poisoned animals in a similar way, and found the salicylic acid only in the serum, the coagulum being free.

Viewing all the evidence together, it seems a probable conclusion that soluble salicylates, when administered internally, enter the vital fluid and circulate there as salicylates, and that salicylic acid itself is probably converted by the alkaline juices of the alimentary canal into a salt, and as such enters the system and exerts its influence on the organism. It is also probable that some of its insoluble salicylates, such as strontium salicylate and bismuth salicylate, undergo slow decomposition in the alimentary canal, yielding their salicylic acid to the alkaline intestinal juices and subsequent absorption. Salicylic acid, although it probably enters into every liquid of the organism, escapes from the body chiefly through the kidneys,† its elimination beginning almost immediately after its ingestion. It appears to be excreted partly as salicylic acid and as a salicylate, partly as salicyluric acid, and it may be also as certain at present unknown educts.

Ugolino Mosso[7] recovered, both in man and animals, practically all of the salicylic acid which had been ingested, from the urine, either in the form of salicylic or salicyluric acid. Fürbringer and Drasche failed to detect it in the fæces, the saliva, the bronchial secretion, or the sweat, but Mussy[8] found it in the saliva, as did also Balz, and Oulmont detected it in the serosity of a blister. It appears in the urine very soon after its ingestion, but its elimination proceeds slowly. Thus, in a case of exstrophy of the bladder it was detected in the urine dripping from the ureters eight and a half minutes after its ingestion (Balz[9]), and it has been found in the urine eight days after the exhibition of the last dose (Byanow[10]). The latter observer also found it in the urine of a normal man as a salicylate twenty-five minutes after its swallowing. The same authority states that it is excreted partly as

* He digested various albuminous substances with salicylic acid, washed them with ether until it would take no more acid, dried, washed with water, and found on analysis salicylic acid largely present in the residue.

† To detect salicylic acid in the urine, add the solution of chloride of iron carefully. At first white phosphate of iron precipitates, then, if the acid be present, a violet color is produced (Kolbe).

salicyluric acid,* partly as a form of salicin, and, he believes, to some extent as oxalic acid. Urine which had been passed some hours after the ingestion of a dose polarized to the left. A. E. Stuart,[11] after so small a dose as nine grains of the acid, saw free, distinct crystals of salicyluric acid in the urine. It is possible that such of the salicylic acid as escapes unchanged from the kidney may, as first excreted, be in the form of a salicylate, but be set free by the phosphoric acid of the urine; at least such would be indicated by the fact that in Balz's case of exstrophy sodium salicylate appeared in the urine twelve minutes before the free acid. The green color of the urine characteristic of the free use of salicylic acid appears to be due to an increase in the formation of indican (S. Wolfberg,[12] M. Robin[13]), or else to pyrocatechin (Sée[14]), and it is not improbable that the pyrocatechin is formed out of the salicylic acid.

General Effects.—When salicylic acid is given to man in doses just sufficient to manifest its presence, symptoms closely resembling cinchonism result. These are fulness of the head, with roaring and buzzing in the ears. After larger doses, to these symptoms are added distress in the head, or positive headache, disturbances of hearing and vision (deafness, amblyopia, partial blindness), and excessive sweating. According to Reiss,[15] decided fall of temperature without alteration of the pulse also occurs; but this is denied by other observers.

The urine may be increased, diminished, or in normal amount during the administration of salicylic acid. After toxic doses it becomes albuminous, and Sée reports a case in which the renal irritation was so severe as to give rise to hæmaturia.

In salicylic acid poisoning, along with an intensification of the symptoms already mentioned, there are ptosis, deafness, strabismus, mydriasis, disturbance of respiration, excessive restlessness passing into delirium, slow laboring pulse, leucocytosis, olive-green urine, and involuntary evacuations. In some cases the temperature has remained about normal, but in others has approached that of collapse. The respiration appears to be almost characteristic: it is both quickened and deepened. In some cases the dyspnœa has been extreme, and given rise to the most violent respiratory efforts. Various local evidences of vaso-motor weakness may supervene, such as rapidly appearing bed-sores at points subjected to pressure, and transitory dark-colored maculæ on various parts of the body.†

In several cases death has probably been produced by the acid. The most conclusive case is that of H. Quincke.[16] The chief post-mortem changes were a breaking down of the blood, congestion of most of the viscera, and ecchymoses on the serous membranes.‡

* Salicyluric acid is a parallel compound to hippuric acid, made by the union of the elements of a glycocoll with salicylic acid.

† For cases, consult *Deutsches Archiv f. Klin. Med.*, xix. 319; *Centralbl. f. Chirurgie*, 1877, 278,—four hundred and one grains of sodium salicylate taken in twelve hours; *London Lancet*, 1876, 2, 681; *Berlin. Klin. Wochenschrift*, 1876, No. 4, 8; and *Bull. Thérap.*, 1877, xciii. 25.

‡ In the case recorded in the *Virginia Med. Monthly*, June, 1877, forty-eight grains of the acid were taken in four hours. The symptoms were violent vomiting, headache, total unconsciousness, and stertorous breathing. Death occurred forty hours after the first

In rare instances even the therapeutic use of salicylic acid has produced severe skin eruptions. The form has been sometimes like that of urticaria, in other cases it has been exanthematous, bullatous, or even purpuric and gangrenous.*

In some cases of salicylic acid poisoning the mental disturbance has been prolonged a week or more. It is stated that upon drunkards the acid acts very unfavorably, violent delirium being a common and early symptom of its influence. There are also some persons whose idiosyncrasies are such that mental disturbance is produced even by moderate doses of the acid. In some cases the delirium is cheerful, in others it is melancholic in type. In the mildest form it is manifested only by a tendency to dream actively and to talk during sleep. In other cases the roaring in the ears soon becomes associated with disturbances of vision, which grow more marked until the patient not only sees objects in false appearances and colors but has absolute illusions. The hallucinations are apt to take the shapes of animals such as are seen in delirium tremens, but there is usually little or no terror, and the troops of images may march to beautiful music. In other cases the delirium amounts to acute mania, with restlessness, violent outcries, and even a fury of fighting (J. Krueg[17]). Mydriasis and amblyopia like that caused by quinine have been noticed in a number of cases, but Gibson and Felkin[18] report excessive myosis, with loss of the light reflexes.

When given to dogs by the mouth in large doses, salicylic acid is said to be usually vomited. According to Laborde,[19] when from four to five grammes of sodium salicylate are injected into the veins of the dog the first result is a slight acceleration of the heart's action and of breathing; this is followed by efforts at vomiting, quietude, loss of muscular strength, with a decidedly ataxic gait, hebetude, stupor, dyspnœa, general convulsions, and death from asphyxia.

Nervous System.—So far as we know, the therapeutic dose of salicylic acid has no distinct action upon the nervous system, unless it be the peripheral ends of the auditory and perhaps other nerves of special sense, the tinnitus aurium caused by it indicating that upon these organs it acts

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dose. Our belief is that either much more of the acid than forty-eight grains was taken, or, what is more probable, death was from some other cause. (See also *Med. and Surg. Reporter*, 1878.) There is no probability that in the alleged case of poisoning reported by Frank Ogston (*Brit. Med. Journ.*, 1883, i. 869) the salicylate had anything to do with the untoward symptoms or result. The case reported by Dixneuf (*Thèse*, Paris, 1878), also that of Empis and Gubler (*Bull. de l'Acad. Med.*, 1877), we have not had opportunity to examine. It is worthy of remark that in the early history of the use of the salicylates disagreeable symptoms appear to have been present much more frequently than of later years, and it is very probable that in many cases such symptoms have been due to the presence of impurities. Thus, *paracresotic acid* has been isolated from commercial salicylic acid by Dunstan. Both it and *orthocresotic acid* have been found by Charteris to be very fatal poisons to the lower animals, producing general paralysis and death from asphyxia. One grain of orthocresotic acid and two grains of paracresotic acid caused death in three hours in rabbits weighing two pounds (*Brit. Med. Journ.*, 1891, i.).

* *Journ. Cutaneous and Genito-Urin. Diseases*, 1896; see especially *Deutsch. Med. Wochenschr.*, 1886.

as does quinine. The symptoms of salicylic acid poisoning indicate that the drug does act, when in overwhelming dose, upon the cerebral cortex; how far other portions of the nervous system are affected is at present uncertain.

According to Sée, neither the reflexes nor the general sensibility, nor the conducting power of the nerve-trunks are sensibly impaired in the lower animals poisoned by a salicylate, but Laborde states that a drachm of the salicylate will produce in a dog profound cutaneous anæsthesia; and Bochefontaine affirms that in the frog the drug depresses the spinal cord, it may be to the point of paralysis.

Respiration.—The respiratory phenomena produced by salicylates in the lower animals are said to be quickening, followed by slowing, of the respiration, with gradual failure until death from asphyxia results. The slowing and final paralysis are probably due to a direct action upon the respiratory centre. The primary quickening has been ascribed with plausibility to irritation of the pulmonary vagi, though it is probable that there is primary stimulation of the respiratory centre.

When, in Köhler's experiments, the pneumogastrics were divided during the period of retardation, the frequency of the respiration was still further lessened. Danewsky[20] practised section of the vagi before exhibiting the drug and during the first stage of accelerated breathing. In the first instance he found that the breathing was only slightly accelerated by the drug; in the second, that the quickened respiration fell to the same slowness that is seen in the unpoisoned animal with cut pneumogastrics. His experiments were too few to be conclusive, but indicate the correctness of his deduction.

Muscles.—According to Charles Livon,[21] salicylic acid has a distinct influence upon the muscle-tissue of the frog, producing a primary increase and secondary decrease of excitability and altering the character of the muscular contractions.

Circulation.—There was at one time a belief not only among clinicians, but also physiologists, that salicylic acid even in small doses decreases the arterial pressure. It seems, however, to be established that whilst toxic doses of salicylic acid do depress arterial pressure, moderate doses exert no such influence; indeed, Danewsky is probably correct in asserting that they increase the arterial pressure by stimulating the vaso-motor centres. The final fall of the arterial pressure is in large part, if not altogether, due to a direct action of the drug upon the heart itself.

E. Maragliano,[22] in a very large number of sphygmographic and sphygmomanometrical studies, found the arterial pressure usually elevated, and never depressed, by therapeutic doses of the drug. In 1879 Hugues Oltremare[23] affirmed that moderate doses of sodium salicylate increased the frequency of the pulse and the arterial pressure, and in this was subsequently confirmed by Danewsky. According to the latter observer, although the force and energy of the cardiac beat are increased by the small dose of the drug, yet the inability of the salicylate to elevate the arterial pressure after section of the spinal cord shows that the main factor in the rise of the blood-pressure is spasm of the blood-vessels due to stimulation of the vaso-

motor centres in the medulla. Köhler, Oltremare, and Danewsky have found that after toxic doses the arterial pressure steadily falls, the heart-stroke becoming weaker and weaker, and finally being extinguished. Köhler, determining that the fall of pressure is not prevented by previous section of the depressors, the vagi, and the cervical cord, logically concludes that it is due to an action upon the heart itself. In Paul Faval's[24] experiments upon the isolated heart of the frog, small doses of salicylic acid had no perceptible influence, although large doses paralyzed the viscus.

Nutrition.—The experiments of Haig,[25] of S. Wolfsohn,[26] of C. Virchow,[27] of E. G. Salomé,[28] of M. Kumagawa,[29] of F. Tausk and B. Vas,[30] and of Bohland,[31] which have been made upon various animals and upon healthy men, are so numerous and concordant in their relations as to prove that in the normal man or animal salicylic acid and its preparations *increase to a very great extent the elimination of urea and uric acid.* In the experiments of Kumagawa, the uric acid was increased in the healthy dog from thirty to seventy-four per cent. There was also marked increase in the elimination of sulphur compounds, although the relation between the elimination of nitrogen and sulphur, which in the normal animal is fixed, was distinctly disturbed.

The question whether this elimination of urea and uric acid is the outcome of an influence upon tissue change or is due to an increased formation of these substances can hardly be answered positively at present. Schreiber and Zandy[32] would seem to be correct in believing that there is increased formation of urea, but the experiments of Lecorché and Salamon indicate that in rheumatism the action of the acid is rather in favoring elimination than increased formation. Thus, these observers found that in acute rheumatism there is under the influence of salicylates an increase both of urea and uric acid, usually lasting three or four days, and then followed by a lessening of the excretion, which in many cases carries the elimination of these substances below the normal.

Closely connected with the subject of the action of salicylates upon nutrition is that of their influence upon temperature. Both in the normal man and in the lower animals, except in rare cases, even the largest therapeutic doses of the salicylates do not lower the bodily temperature (Fürbringer,[33] Gedl,[34] Danewsky, and Sée). It is probable, however, that salicylic acid, like quinine, has, in non-toxic doses, some control over thermo-genesis in health. Thus, in one or two experiments upon himself, North[35] found that the acid exerted a decided influence in preventing the rise of bodily temperature normally caused by exercise.

In fever the antipyretic action of the salicylates is very pronounced; usually in about fifteen minutes after the administration of the drug a profuse sweat appears, which is soon followed by a fall of temperature that, according to Justi,[36] reaches its maximum in about six hours.*

* The statements in regard to the action of salicylic acid on the pulse in fever vary so much as to suggest that when any decided lessening of the cardiac beat does occur, it is dependent upon the fall of temperature. Thus, Garcin (*Journ. de Thérap.*, 1876, 25),

The sweating is profuse and exhausting, amounting, according to Ewald,[37] not rarely to seven hundred and fifty grammes. The perspiration can scarcely be the chief factor in the reduction of temperature, as there appears to be no relation between its amount and the degree of the fall, and it usually ceases before the latter reaches its maximum.

In what way the fall of temperature is produced we have at present no knowledge, since in the only experiments upon the subject—those of Hobart A. Hare,[38]—the doses employed were not sufficient to give positive results.

Especially was this true in the experiments made upon animals suffering from fever. Indeed, there was not in those animals any fall of bodily temperature under the influence of the salicylic acid administered. To attempt to reason from the results reached as to the method of the action of salicylic acid when it does cause fall in bodily temperature seems futile.

SUMMARY.—Salicylic acid, and to a less degree the salicylates, are irritant to the mucous membranes, though it is probable that the disorder of digestion produced by the acid and its salts is chiefly due to their inhibiting the activity of the digestive ferments. Salicylic acid is readily absorbed and probably circulates in the blood as a sodium or other salicylate; it is eliminated partly unchanged as a salicylate, partly as salicyluric acid, the green discoloration of the urine being due to indican, or perhaps to pyrocatechin, which may be an educt from the acid. The elimination both of urea and uric acid is increased by the salicylates. It is probable that this increase is due to some action upon general protoplasmic chemical activities, though it may be that the salicylates increase chiefly the elimination of formed urea and uric acid. In full doses salicylic acid causes symptoms resembling those produced by quinine, but after larger doses there are mydriasis, marked disturbance of respiration, great nervous prostration, delirium, dyspnœa, and, if the dose has been large enough, death by respiratory paralysis. Moderate therapeutic doses appear to have no powerful influence upon the circulation, such physiological evidence as we have indicating that they increase arterial pressure somewhat by exciting the vaso-motor centre and directly increasing the cardiac force. In overdoses salicylic acid causes fall of the arterial pressure, partly by a direct action upon the heart. Our knowledge of the action of the acid upon the nervous system is very imperfect, but it seems to be a depressant of the motor nervous centres. Moderate doses increase the frequency of the respiration, probably in part by an action upon the peripheral pneumogastrics, but chiefly by a direct influence upon the respiratory centre. Toxic doses paralyze the respiratory centre. The action of salicylic acid upon the temperature of normal man is slight and inconstant, unless toxic doses be given; in fever its antipyretic influence is pronounced, but we have no exact knowledge as to the method.

THERAPEUTICS.—The salicylates were originally introduced by E. Butt[39] for the purpose of reducing temperature in typhoid and other

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Oulmont (*Le Progrès Méd.*, 1877, 587), and Moeli (*Deutsches Archiv*, xvii. 592) have all observed the pulse-rate to fall with the fever-heat, while L. Schroeder affirms that after moderate doses the pulse is slackened, after large ones quickened, and Ewald and other observers state that it is usually not affected.

fevers, but have been superseded by various agents which are not only more effective but more sure and less disagreeable in their action. In 1876 Stricker,[40] of Berlin, using salicylic acid as an antipyretic in acute rheumatism, discovered the extraordinary antirheumatic influence of the salicylates, which have come to be the standard remedy in all forms of rheumatism. Of all known agents the salicylates are possessed of the most power for good in acute *inflammatory rheumatism*, in subacute or *muscular rheumatism*, in *rheumatic neuritis* and other irregular forms of rheumatism, and are often temporarily of great service even in *chronic rheumatism*. In *gout* the powers of the salicylates for good are much less than they are in rheumatic diseases, but in all of the regular forms of gouty diseases a salicylate should be tried, and will often be found to be of temporary service; they usually combine well with colchicum. Clinical experience has demonstrated that in these various conditions the salicylates seem to be palliative rather than curative; in other words, that they for the present modify and overcome the rheumatic symptoms, but that they exert no permanent influence upon the diathesis which is the basis of the disease. In septic simulations of rheumatism, such as *gonorrhœal rheumatism*, and in *rheumatoid arthritis*, the salicylates are rarely of any service. In *rheumatic angina* and in *quinsy*, which seems to have some relation to the rheumatic diathesis, the salicylates often do good; they are, however, of no value in *diphtheria*. At one time the salicylates were used to a considerable extent in *chronic cystitis* and *chronic pyelitis* for their influence upon the inflamed mucous membrane, but at present are rarely employed.

The salicylates have been used to some extent as antiperiodics, but the general drift of experience coincides with that of Helley, who found salicylic acid to fail in severe cases of malaria, and to require a longer time for the cure of mild cases than does quinine.

As alterative diuretics the salicylates have been commended by Armin Huber[41] and other clinicians[42] in the treatment of *acute* and *chronic pleurisy* with watery effusions.

Use as an Antiseptic.—Salicylic acid was originally brought to the notice of the profession on account of its inhibitory influence on putrefaction. Kolbe[43] found that 0.04 per cent. had great influence in preventing souring of milk. Bucholz states that 0.15 per cent. is sufficient to prevent the development of bacteria in ordinary organic mixtures, and that the influence of 0.005 per cent. is plainly visible; 0.3 to 0.4 per cent. of the acid killed bacteria in vigorous growth. The sodium salicylate was about equal to the pure acid, 0.4 per cent. destroying the bacteria. In the preservation of urine, Meyer and Kolbe[44] found that one part of salicylic acid to two thousand parts of urine was sufficient to prevent putrefaction.

Salicylic acid has been used to a considerable extent in the preparation of beer and wine, and for the preservation of various articles of food. On February 7, 1881, the French government interdicted this use, and

in 1885 a commission[45] appointed by the Academy of Medicine of Paris, at the suggestion of the Minister of Agriculture, reported that it is proved that the prolonged employment of even very small amounts of salicylic acid is dangerous, and that in susceptible individuals, and especially in aged persons, it is apt to cause disorder of digestion and renal disease.

There can be no doubt that salicylic acid is capable of accomplishing much in antiseptic surgery, but it is at present rarely used.

Locally, salicylic acid is a distinct stimulant; in the experiments of Hodara[46] its prolonged contact with the skin caused swelling of the epidermis, followed after a time by desquamation or exfoliation, the cast-off flakes having a thickness in direct proportion to the strength of the preparation used. When the application was continued for some days œdema and necrosis of the epithelium resulted. It is also much used by dermatologists in various skin diseases when there is pronounced thickening of the epidermis.

In 1875 Hirt called attention to the irritation of the pulmonic mucous membrane in workmen engaged in the manufacture of salicylic acid, and various specialists have employed it as a local remedy in the treatment of chronic laryngeal and pulmonic inflammations.

ADMINISTRATION.—In the administration of salicylic acid or its salts it is of importance to exercise care. The acid itself is too irritant to be exhibited in doses of over five grains, and if used should always be in capsules.

Sodium Salicylate (SODII SALICYLAS, U. S.) is a freely soluble salt, very unpleasant to the taste, but efficient. *Ammonium Salicylate*, non-official, is also freely soluble, is somewhat less unpleasant to the taste than the soda salt, and for most purposes is preferable to it. The *Strontium Salicylate*, non-official, is a valuable compound, which slowly yields up its salicylic acid in the alimentary canal, and has the great advantage of being much less apt to derange digestion. It is, however, too slow in its influence to be used when a quick, powerful effect of the salicylates is desired. When small doses only are to be employed, the ammonium salicylate may be combined with the strontium salicylate in capsules. In some cases five grains of each salt thus administered are well borne by the stomach. When, however, salicylates are to be employed in large doses, they must be given in solution, and should, unless under very exceptional circumstances, be administered in milk, and preferably not after a meal, lest they interfere immediately with gastric digestion. When large doses of the salicylates are to be taken, strychnine and often tincture of digitalis should be given with them to overcome their depressing effects. In severe cases a much better result is usually obtained by administering large doses of the salicylates with frequent interruptions than by giving the salicylates repeatedly in small quantities. Often the salicylates are best given every other day. The *Oil of Gaultheria* is as prompt in its influence as is the ammonium salicylate, and may often be combined with it or used by itself.

The maximum daily dose of the salicylates may be set down as one hundred grains (6.5 Gm.), though in rare cases only is it well to give over seventy-five grains, and usually less will suffice. In chronic cases thirty grains (2 Gm.) is an average dose. The occurrence of tinnitus aurium is an evidence of systemic intoxication, and should be the signal for the lessening of the dose.

OLEUM GAULTHERIÆ—OIL OF GAULTHERIA. U.S.

Oil of gaultheria is a very volatile, slightly straw-colored liquid, of a penetrating peculiar odor, ninety per cent. of which is *methyl salicylate.*

Methyl salicylate is a substitution-compound in which one atom of the hydrogen of salicylic acid has been replaced by a molecule of methyl, CH_3. The formula of salicylic acid is $C_7H_6O_3$; of methyl salicylate, $C_7\left\{\begin{matrix}H_5\\CH_3\end{matrix}\right\}O_3$.

When oil of gaultheria is taken into the animal system, one atom of carbon and two atoms of hydrogen in the methyl are removed by oxidation, and $C_7\left\{\begin{matrix}H_5\\CH_3\end{matrix}\right\}O_3$ becomes $C_7H_6O_3$. $C_7\left\{\begin{matrix}H_5\\CH_3\end{matrix}\right\}O_3$ has an atomic weight of 152, while the atomic weight of $C_7H_6O_3$ is 138: so that the administration of one hundred and fifty-two grains of methyl salicylate ought to be equivalent to the giving of one hundred and thirty-eight grains of salicylic acid.

As one hundred and sixty-nine grains of oil of gaultheria contain one hundred and fifty-two grains of methyl salicylate, they should be equivalent to one hundred and thirty-eight grains of salicylic acid.

Oil of gaultheria, *Oil of Sweet Birch* (OLEUM BETULÆ VOLATILE, U. S.), and the *Methyl Salicylate* prepared synthetically (METHYL SALICYLAS, U. S.) are so similar in composition that they *probably* have the same action upon the human economy, but this is not *certain*, and the apothecary should always put up the exact drug prescribed.

The question whether the natural salicylic acid of the oil of gaultheria has any different physiological action from the artificially prepared but chemically identical acid has been elaborately investigated by B. J. Stokvis,[47] who reaches the conclusion that there is a marked quantitative difference, the natural acid being distinctly less poisonous than the artificial,—a circumstance which he believes to be due to the superior osmotic properties of the natural acid, causing it to be more rapidly eliminated.

Oil of gaultheria is more irritant than the other salicylates, but is capable of causing all the ordinary symptoms of salicylic acid poisoning.

An ounce produced violent gastro-intestinal irritation, followed by convulsions, coma, and death in fifteen hours, Pinkham.[48] In Juvet's[49] case a half-ounce caused death; but the same amount has been recovered from (Gallaher[50]), probably on account of the vomiting induced. H. C. Wood and Hobart A. Hare[51] have shown that the physiological action of gaultheria is the same as that of salicylic acid, and that therapeutic doses are entirely decomposed in the system, although toxic amounts may escape in part unchanged.

Oil of gaultheria may be administered in emulsion or in capsules in doses of from ten to fifteen minims (0.6–1 C.c.), repeated according to circumstances. We have given as high as one hundred and fifty drops of it in twenty-four hours, though few persons will bear more than half this amount.

The continuous soaking of rheumatic joints in oil of wintergreen is often of service. Linossier and Lannois[52] have found that absorption through the skin occurs so quickly that the salicylic acid can be detected in the urine within half an hour after the application.

SALICINUM—SALICIN. U.S.

The glucoside *Salicin* is obtained from the bark of the willow (*Salix*) and other trees. It occurs in tabular crystals or in white, shining needles, soluble in about thirty parts of cold water, very soluble in hot water.

The physiological action of salicin is very feeble, since in Ranke's case three ounces of it produced no notable effect. It is rapidly absorbed and almost as rapidly decomposed in the system, its educts appearing in the urine fifteen to thirty minutes after its ingestion. According to Husemann,[1] a portion of it fails to undergo change, salicin, as well as saligenin and salicylic acid, appearing in the urine of men who have taken it freely. Indeed, in Falck's experiments upon the dog, the largest portion of salicin injected into the blood escaped from the kidneys unchanged.

According to Scarpetti,[2] salicin inhibits functional activity of the red and white blood-corpuscles similarly to, but less powerfully than, quinine.

The assertion of Maclagan,[3] that salicin is a specific in acute rheumatism, although it received some confirmation from H. Senator,[4] has not stood the test of time. It is probable, as believed by Senator, that any therapeutic activity possessed by salicin depends upon its conversion in the system into salicylic acid, and as this conversion is very slow and imperfect,* it is plain that the remedy must be very inferior to salicylic acid. The dose recommended by Senator is two to two and a half drachms (8–10 Gm.).

SALOL, U. S., is a white, tasteless, insoluble crystalline powder, of a faintly aromatic odor.

Salol is a derivative of salicylic acid, one atom of the hydrogen of the acid having been replaced by phenol. It belongs to the aromatic ethers, and may be considered chemically as a phenol salicylate. Originally prepared by Von Nencki, of Berne, it was introduced into medicine by H. Sahli.[1]

Salol is broken up by alkalies into its constituents, so that in the upper intestinal tract it undergoes decomposition, yielding about thirty-

* Senator has detected salicylic acid in the urine sixty hours after the ingestion of a single dose of salicin.

six per cent. of phenol and sixty-four per cent. of salicylic acid.* It is capable of producing tinnitus aurium and other evidences of salicylic acid action as well as the black urine and symptoms of carbolic acid poisoning. It is said to be less powerful as a poison than are its ununited ingredients, probably because it is broken up slowly and escapes in part unchanged. Kumagawa[2] has found that it increases nitrogenous elimination.

Salol has been used to a considerable extent as a substitute for salicylic acid in acute and subacute *rheumatism*, but it is evident that a large amount of carbolic acid which it carries with it must seriously affect its influence, and clinical experience shows that it affords only a very uncertain method of administering salicylic acid. According to the researches of Lesnik,[3] it is so feebly germicidal as to have practically no influence upon the bacteria. The products of its decomposition in the intestines are, however, very active germicides, and it would appear, therefore, to be one of the best, if indeed not the most effective, of the intestinal disinfectants, and is much used as such in *typhoid fever*, *intestinal indigestion*, and other complaints. The uncertainty of the action of this class of intestinal disinfectants is, however, well shown by the experiments of Kumagawa, who found that in animals large doses of salol failed to produce lessening of the urinary indican or of the intestinal bacteria.

Externally, salol has been used as an antiseptic by surgeons, but is of little value. The ordinary dose is ten grains (0.6 Gm.), but one hundred grains a day have frequently been given without producing any serious effect; evidence that a large proportion of the salol escapes unchanged from the intestines, since that amount of the drug represents thirty-six grains of carbolic acid. As an intestinal disinfectant it should be administered in capsules one hour after meals.

Death is said to have been caused by fifteen grains of salol,[4] but this seems incredible. Hesselbach calls attention to the influence that carbolic acid has upon the cortex of the kidneys, and believes that the long-continued use of even small doses of salol is dangerous when those organs are diseased.

Of the various other compounds of salicylic acid which have been produced for use in practical medicine, a few are of sufficient importance to require mention here.

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* Ewald affirms, as the result of experimental research, that salol is not decomposed in the stomach, but immediately upon its entrance into the intestines, and that the products of decomposition appear almost at once in the urine in the form of salicyluric acid, which yields a red precipitate with ferric chloride. Ewald proposes taking advantage of this fact in order to determine the rate at which food passes from the stomach. The urine of seven persons in sound health afforded the salicyluric acid reaction in from one-half to three-quarters of an hour after the ingestion of the drug, but in seven cases of gastric dilatation with weakness of the muscular coat of the stomach two to three hours were required. More recent clinical experiments, however, throw great doubt upon the value of the test (see *Berlin. Klin. Wochensch.*, 1889, xxvi. 975).

ASPIRIN, a combination of salicylic acid and acetyl, occurs in white, crystalline, insoluble needles, of an agreeable taste, which undergo decomposition in alkaline fluids with the separation of salicylic acid, and are therefore changed by the intestinal fluids. Aspirin has been used in the same dose and for the same purposes as sodium salicylate, and is affirmed by Julius Wogulmuth,[5] by Witthauer, and others to be extremely effective in *rheumatism* and to have very little influence upon the digestion. It has not been sufficiently long in use for its value to be determined.

SALOPHEN, *Acetylparamidophenyl*, contains 50.9 per cent. of salicylic acid, occurs in white, crystalline, insoluble leaflets, and is said to undergo decomposition in alkaline solution. Siebel states that it yields salicylic acid in the alkaline intestinal juices. It has been largely used by various German clinicians in all forms of *rheumatism*, and it is alleged that it is almost equal in this disease to the ordinary salicylates and much less disturbing to the digestion. Daily dose, forty-five to seventy-five grains (3–4.85 Gm.).

BETOL of Sahli,[6] or *Naphthalol* of Kobert, is the β-naphtol ether salicylate, and occurs in small, white, resplendent, almost tasteless crystals, insoluble in water. It is a compound analogous to salol, but having the base of naphtol instead of phenol, and yielding, in the intestinal juices, salicylic acid and naphtol. It contains ten per cent. less salicylic acid than does salol, and has the further disadvantage of possessing a much higher melting-point, and therefore of splitting up less readily into its component parts. It is of very little value in *rheumatism*, but has been considerably used as an intestinal disinfectant, and is especially recommended by Kobert in *gonorrhœal* and other forms of *cystitis*.

BENZOINUM—BENZOIN. U. S.

The concrete juice of Styrax Benzoin, a large tree, native of Siam. The drug is said to be obtained by incising the tree and allowing the juice to harden as it exudes. The finest specimens of benzoin consist of tears agglutinated together ; the poorest, of brown or blackish masses without tears. The fracture is resinous, the surface of the tears smooth and whitish, the odor fragrant, the taste at first very slight, afterwards somewhat acrid. The chief constituents of benzoin are resin and benzoic acid ; cinnamic acid is also frequently present, and is said to be especially found in the white tears.

Benzoic Acid (ACIDUM BENZOICUM, U. S.) is obtained by sublimation of gum benzoin. As thus prepared, it is in white feathery crystals, of a silky lustre, a warm, peculiar taste, and a fragrant vanilla-like odor, due to the presence of a volatile oil, the pure acid being inodorous.

Benzoic acid is widely distributed through the vegetable kingdom, constituting the peculiar principle of all true balsams, and is occasionally present in the urine of grass-eating animals. It is a normal constituent of castor, and has been de-

tected by Seligsohn[1] in the suprarenal capsules of an ox. It is used considerably in the arts, and for this purpose is prepared from the allied hippuric acid of horse urine, and also, it is said, from naphtalin: these forms of the acid should never be used medicinally.

PHYSIOLOGICAL ACTION.—*Local Action.*—Benzoic acid, unless in large quantities and pure, is scarcely irritant to mucous membranes, on which, however, it exerts a distinct alterative influence. As a germicide it is quite active.

Absorption and Elimination.—Benzoic acid is absorbed rapidly, and, as was first discovered in dogs by Wöhler, and afterwards in man by Ure,[2] it is eliminated chiefly from the kidneys, united with nitrogenous atoms, as *hippuric acid.** It has not yet been clearly made out where the nitrogen necessary for the formation of the hippuric acid is obtained. Kuhne and Hallwachs thought that the conversion occurred in the liver; but the researches of Meissner and Shepard[3] appear to show that it really takes place in the kidneys.

The conversion does not happen in the intestines or in the blood, since after the exhibition of large doses of benzoic acid it alone can be detected in the blood; and after the administration to rabbits of large amounts of hippuric acid by the mouth, only traces of the latter, with large quantities of benzoic acid, can be found in the blood, although the hippuric acid appears in the urine;† further, moderate amounts of hippuric acid injected into the blood cause severe symptoms of poisoning, which is not true of benzoic acid. When benzoic acid is injected freely into the blood, a portion escapes through the kidneys unchanged.‡ G. Bunge and O. Schmiedeberg have also found that in the dog with renal arteries tied no conversion of benzoic into hippuric acid occurs, but that tying of the ureters does not interfere with the change. They have also succeeded in converting benzoic into hippuric acid by passing blood containing benzoic acid, with or without glycocoll, slowly through the kidneys, removed from the body directly after death. From some of their experiments it would seem that the blood-corpuscles play an important *rôle* in the process, as when serum freed from blood-corpuscles was used, at most only a trace of hippuric acid was formed. According to Meissner and Shepard, sometimes the benzoic is converted into *succinic* instead of hippuric acid in man, and in chickens it is habitually changed into new products, one of which is nitrogenous.

General Effects.—The influence of benzoic acid upon the general system is very slight. The largest therapeutic doses never produce any symptoms, unless it be those of slight gastric irritation; a half-ounce of

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* Gusseron found hippuric acid in the urine of a new-born child when benzoic acid had been given to the mother just before the birth (*Hoffmann und Schwalbe's Jahresb.*, 1879, 283). The experiments of Von Schrader and of Mosso (*Arch. Exper. Path. u. Pharm.*, 1889, xxvi.) seem to show that the whole of the ingested benzoic acid escapes with the urine.

† For a general summary and latest information, see paper by Van de Velde and Stokvis (*Arch. f. Exper. Path. u. Pharm.*, xvii. 189). V. Poulet (*Bull. Soc. de Méd. Prat.*, 1888) uses the *hippurate of lime and lithia*, affirming that they are much superior to the benzoates in *ammoniacal cystitis*.

‡ According to the experiments of Th. Weyl and B. von Anrep, if benzoic acid be given to man or animals in a febrile state a much larger proportion of it than usual is eliminated unchanged (*Hoffmann und Schwalbe's Jahresb.*, 1881, 447).

the acid taken by Schreiber in two days caused only an increased rapidity of the pulse-beat and moderate disturbances of digestion.

W. Grube[4] states that in massive doses (1 to 5766 of the animal's weight) it produces intoxication, with disturbance of circulation and respiration, and paralysis of the hind feet, and that the antipyretic influence of benzoic acid is greater than that of salicylic acid.

Nutrition.—Some authorities have believed that benzoic acid distinctly affects nutrition, but the testimony as to the action of the acid upon the elimination of urea and uric acid is so contradictory as to indicate that it has no constant powerful influence upon protoplasmic activities or upon nitrogenous elimination.

Ure, Leroy d'Etiolles, and Debouy (quoted by Stillé) affirm that the uric acid is very much diminished or altogether absent, while Garrod[5] and Keller[6] assert that its quantity remains normal. Again, Garrod affirms that the urea is very much diminished in quantity, Keller and Meissner and Shepard declare that it is not affected, and in the elaborate experiments of Carl Virchow,[7] sodium benzoate caused a decided increase of the nitrogenous elimination from the kidneys.

It is commonly asserted by clinicians that the acidity of the urine is increased by the administration of benzoic acid, and it is probable that the disappearance of uric acid crystals from the urine under the influence of the drug is due to the conversion of insoluble uric into soluble hippuric acid. W. W. Ashhurst[8] asserts as the results of experiments made with sodium benzoate, that this salt does not increase the acidity of the urine, and that the mistake of clinicians has arisen from the fact that in cystitis the urine has its acidity increased by the drug because the ammoniacal fermentation is checked by the benzoic acid.

Antiseptic Influence.—In April, 1872, Dougall[9] announced that benzoic acid is an active antiseptic. Since that time, numerous experiments have been made by E. Salkowski,[10] Grube, Bucholtz,[11] and Fleck,[12] with the unanimous result of ascribing to benzoic acid a first rank in destroying bacteria and preventing putrefaction. In most of these investigations benzoic acid was shown to be much more active than salicylic acid. Bucholtz found that 0.02 per cent. of benzoic acid has a very perceptible effect upon the development of bacteria, and 0.1 per cent. inhibits their growth entirely; also that the sodium benzoate is no less powerful than the pure acid. Kumagawa determined that benzoic acid acts powerfully as an intestinal antiseptic, notably reducing both the indican in the urine and the number of the bacteria in the intestines.

THERAPEUTICS.—Benzoic acid is a valuable remedy in subacute *nasal and respiratory catarrhs*, also in *chronic bronchitis*. As an antizymotic it is considerably used by the Germans in *diphtheria*, *erysipelas*, and allied diseases. Senator,[13] of Berlin, alleges that in daily doses of about three drachms it is equal in its action in *acute rheumatism* to salicylic acid.

Ure first suggested the employment of benzoic acid in *uric acid gravel* and *calculus*, because, as he thought, it diminished the excretion of uric acid ; and Golding Bird subsequently asserted that his clinical experience had shown the value of benzoic acid in *uric acid diathesis*. It certainly is often very effective in causing uric acid crystals to disappear from the urine. In the *phosphatic urine* of *vesical catarrh* benzoic acid often acts most happily : it checks fermentation in the urine, aids in the solution of the phosphates, and acts upon the mucous membrane of the bladder as an alterative antiseptic. In *ammoniacal cystitis* the drug is of great value. It is also said often to act very happily in acute *gonorrhœa*.[14]

Benzoic acid has the property of preventing animal fats from becoming rancid, and is therefore much used as an addition to ointments. Moreover, it exerts a peculiar, often very beneficial, stimulant action upon the skin, and is very useful in such conditions as *chapped* hands, lips, or nipples, and even in *fissure* of the *anus*.

There would seem to be no doubt that benzoic acid may be substituted for carbolic or salicylic acid in antiseptic surgery. Under the name of *balsamum traumaticum*, a preparation practically the same as the compound tincture of balsam was formerly much used as a vulnerary. The practice has gone out of vogue, but the discoveries concerning antisepsis show that it was well founded.

Administration.—Gum benzoin is never used itself, but is exhibited in the form of the tincture (Tinctura Benzoini—twenty per cent., U. S.),—dose, one-half to one fluidrachm (2–4 C.c.) ; and of the compound tincture (Tinctura Benzoini Composita—twelve per cent., U. S.), used in chronic *bronchial catarrh*,—dose one to two fluidrachms (4–8 C.c.). Adeps Benzoinatus, two per cent., U. S., contains only enough of the benzoin to preserve the lard, and is employed as the basis of ointments. Dose of benzoic acid, ten to thirty grains (0.6–2 Gm.) in capsules ; of sodium benzoate (Sodii Benzoas, U. S.), twenty to fifty grains (1.3–3 Gm.).

ANTIPYRIN—PHENAZONUM. Br. Ph.

Phenyl-dimethyl-iso-pyrazolone or antipyrin was discovered by Ludwig Knorr, of Munich, and first experimented with by Filehne,[1] of Erlangen. It is a grayish or reddish-white crystalline powder, of a slightly bitter taste, soluble in fifty parts of ether, much more so in water, ten parts of it being dissolved in six parts of cold water, and also very soluble in alcohol and chloroform.

Physiological Action.—*Local Action.*—The local action of antipyrin is not thoroughly understood. It is somewhat irritant, and it is alleged that it acts with sufficient power upon the sensory nerves to be useful as a practical local anæsthetic, especially when applied to the laryngeal or nasal mucous membrane. It is also stated that antipyrin is a very active hæmostatic, a forty per cent. solution causing when applied locally most active contraction of all the small blood-vessels.

Saint-Hilaire [3] affirms that the anæsthesia produced by antipyrin is complete and generally lasts from one to two hours; that the sensibility to touch and also to heat and cold is destroyed, the thermal sense returning first; also, that the solution must not be of less strength than thirty per cent., twenty per cent. solutions having no anæsthetic effect. Huchard and Henocque (quoted by Armand) state that when they cut off the feet of guinea-pigs and put the stumps into a solution of antipyrin, tincture of ferric chloride, etc., the bleeding was arrested most quickly by the antipyrin.

Antipyrin is probably absorbed with rapidity and appears to be usually eliminated promptly and rapidly through the kidneys, although some observers have failed to find it in the urine for several hours after its ingestion.

I. I. Hage [3] was unable to find the drug in the sweat or the saliva, but it has been found in minute quantities in the milk of nursing women both by Pinzani,[4] and by Fieux.[5] Armand states that it can be continuously detected in the urine from twenty-five minutes to thirty-six hours after its ingestion, although most of it is eliminated in the first twelve hours. Perret and Givre [6] found that urinary elimination begins in the adult or in the child three-quarters of an hour to an hour after the ingestion, but that the child eliminates the antipyrin more rapidly than the adult. According to Maragliano,[7] the elimination is at its height in four hours, and continues for a day and a half. The urine is sometimes increased, sometimes diminished, in quantity; it is normal in appearance, and never contains albumin or sugar.

There is some reason for believing that a portion of the antipyrin undergoes decomposition in the body, although we have not sufficient information upon the subject for any positive conclusion.

Capitan and Gley [8] found that the action of the drug is much less intense when it is thrown into the mesenteric vein than when it is given by injection under the skin or into the peripheral vein. Their theory, that the liver retains or modifies antipyrin, is made more plausible by the researches of Wera Iwanoff,[9] who finds that the liver-cells of frogs poisoned with antipyrin undergo very pronounced changes in their nuclei and protoplasm. The statements of Iwanoff are especially important in connection with the known effect of antipyrin upon urea elimination. Disturbances of the hepatic function may be at the basis of the inhibitive action of the drug upon urea formation.

General Effects.—When given to the normal man in doses of from ten to twenty grains, antipyrin produces usually no distinct symptoms. If, however, it be administered in a larger dose, and especially if it be given in the continuous dose, so as to accumulate in the system, it causes languor, malaise, and a peculiar cyanotic pallor of the face, with failure of the pulse. Vomiting sometimes occurs. The symptoms which have in a number of cases followed large doses are very curious, and some of them difficult of explanation. Prominent among these symptoms is an eruption on the skin, which may occur without constitutional disturbance, but is often accompanied thereby. In its most typical form it consists of small, reddish, irregularly circular spots, resembling somewhat those of measles, and arranged in patches separated by sound skin. The red color usually

disappears on pressure, leaving a brown pigmentation, which also comes into view during the fading of the exanthem, and ordinarily continues five or six days. In some cases the eruption is erythematous ; not rarely it resembles an urticaria in which the white wheals may be made very prominent by a wide-spread, deep crimson blush.

In a case reported by Spitz[10] the whole surface of the body was covered with bullæ, which, becoming confluent, involved the skin in a universal desquamative inflammation. Very frequently the antipyrin rash is accompanied by wide-spread œdema, which may be most pronounced in the extremities, but is especially prone to involve the face, causing great swelling, and even closure of the eyes. The mucous membranes may share in the irritation. Violent catarrhal conjunctivitis is not very rare, whilst coryza and laryngitis have been noticed.*

The marked rise of temperature and disturbance of the circulation which often accompany the antipyrin eruption are probably due to the irritation of the skin and the subdermal tissue, since, when the antipyretic eruption takes the form of an urticaria, the itching, sighing, hysterical unrest, and dyspnœa, which are apt to accompany urticarias not due to antipyrin, have been very pronounced.

In a number of cases of antipyrin-poisoning there have been violent nervous symptoms, which seem to be a direct outcome of the action of the poison. The vomiting, which is sometimes accompanied by abdominal pain, may be looked on as an evidence of local irritation ; but this is hardly the case with giddiness, somnolence deepening into coma and passing into profound stertorous unconsciousness, with dilatation of the pupils and epileptiform convulsions,—all of which have been noted. The unrest, excitement, and violent tremblings not rarely seen seem also to be directly produced by the drug.† H. M. Briggs[11] reports blackish urine with albumin and blood-corpuscles in antipyrin-poisoning.

As illustrative of the symptoms of antipyrin-poisoning may be cited the case reported by F. Spitzer,[12] in which a man, aged twenty-four, shortly after taking one hundred and twenty grains of antipyrin during an hour, complained of violent pain in the belly, and vomited freely ; an hour later he was found in a condition of great excitement, screaming, champing his teeth, with a red face, much swollen conjunctiva, and cold extremities ; the pulse was 108 per minute, rhythmical, with strong heart-impulse ; the respiration 38. There was præcordial anguish, pain in the stomach, and marked tremors, with exaggeration of the tendon-reflexes. Fifteen hours after the poisoning he was seized with a sudden chill, with marked cardiac failure, from which, however, he recovered.

The symptoms produced by antipyrin upon the lower animals resemble those caused in man, except in the absence of dermal irritation and its secondary results.

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* For cases, see *London Lancet*, 1888, i. ; *British Med. Journ.*, 1888, i. ; also 1892, i.

† See *Berlin. Klin. Wochensch.*, 1889, xxvi. ; *Med. News*, 1889, liv. ; *Correspond.-Blatt.*, 1888.

According to the observations of Leon Arduin,[13] Demme,[14] Coppola,[15] Simon and Hock,[16] and others, in the frog, in moderate toxic doses (half to one centigramme), it causes convulsions, with opisthotonos, and a very marked increase of reflex activity. In the earlier stages of this condition the animal is cataleptic, and L. Blumeneau[17] affirms that there is a primary stage of quiet with diminished reflex activity. If given in overwhelming amount, antipyrin causes in the frog immediate quiet, muscular relaxation, with loss of reflex activity, deepening into complete paralysis and death. In mammals the chief symptoms of antipyrin-poisoning are ataxy, paraplegia, hurried respiration, convulsions with general rigidity, dilated pupils, unconsciousness, and fall of temperature, ending in death, which seems to be due to failure of respiration.

Nervous System.—The quietness produced by therapeutic doses of antipyrin, and the cerebral symptoms of antipyrin-poisoning, show that the drug has a peculiar influence upon the cerebral cortex. Simon and Hock believe that their experiments prove that the special senses are first stimulated and then paralyzed. The convulsions of antipyrin-poisoning are probably in part epileptiform (*i.e.*, of cerebral origin) and in part tetanic (*i.e.*, of spinal origin), though the testimony concerning this matter is contradictory.

Blumeneau and Batten and Bokenham[18] state that section of the cord does not prevent the occurrence of the convulsions in the posterior segment of the body; while Coppola and Simon and Hock state that it has such action. Either the first-named observers failed to make complete section or else both cerebral and spinal convulsions are produced by the drug.

Our knowledge of the action of antipyrin upon the spinal cord is very incomplete. We do not certainly know whether the alleged primary decrease of reflex activity (Blumeneau), or the characteristic increase of reflex activity (various observers), or the final abolition of reflex activity are or are not of spinal origin, although it is *probable* that in toxic doses the drug acts as a *primary stimulant and a secondary depressant of the spinal cord.*

Chouppe[19] states that the drug even has the power of suspending the strychnic convulsions. If the observation of Blumeneau—that in a frog with the cerebral hemispheres removed antipyrin produced slowness of reflex reaction, which immediately disappeared upon section of the spinal cord high up—be correct, the primary reflex depression is probably cerebral.

There seems to be no doubt that antipyrin *paralyzes both the motor and the sensory nerves.*

Lepine[20] has noticed that if access to a motor nerve be shut off, such nerve, after death from antipyrin, will be distinctly more active in its response to stimuli than is the implicated nerve; whilst Simon and Hock noted in frogs killed with antipyrin the motor nerves absolutely paralyzed, and have also demonstrated the influence of the drug by bringing it in local contact with an exposed nerve. These latter observers further confirm the earlier work of Coppola, and it seems to be proved that when applied locally, or given internally, antipyrin is a distinct *de-*

pressant of the sensory nerve-trunks. Simon and Hock state that in the beginning of the convulsive stage animals can be operated upon without the use of an anæsthetic.

How far the vaso-motor and other nerves connected with the involuntary movements of the body are influenced by antipyrin is at present uncertain, although there is some reason to suspect that the drug acts upon them as it does upon the nerves connected with voluntary life.

According to Batten and Bokenham, when locally applied to the exposed intestine, antipyrin prevents the peristaltic wave which is normally produced by the application of common salt, although it does not check the annular contraction at the point of irritation; an effect which seems explainable only by the supposition that the intestinal nerves and not the intestinal muscles are paralyzed by the drug.

Muscles.—According to Devraux-Armand,[21] the muscular stiffness of advanced antipyrin-poisoning, when the poisoning is fatal, passes directly into post-mortem rigidity. Moreover, in Armand's researches the contractions of muscles taken from the body of animals killed with antipyrin were much more powerful and prolonged than were those produced by the same amount of stimulation in the normal muscle.

Circulation.—Demme, Arduin, Armand, Henry Casimir,[22] and Cerna and Carter[23] have separately determined by experiment that in moderate doses *antipyrin increases the arterial pressure*, while *toxic doses lower the pressure.* The cause or causes of the rise have not yet been fully determined; it occurs in curarized animals, and is therefore independent of any action of the drug upon the respiratory centre. According to Cerna and Carter, it is not prevented by previous section of the pneumogastric nerves and of the spinal cord, and the pulse-waves accompanying it are of extraordinary size and height. It would appear, therefore, that it is at least in part due to *a direct stimulation of the heart.* Unfortunately, however, the evidence which we have at present is so contradictory that no positive conclusions can be drawn as to the effect of the largest therapeutic dose of antipyrin upon the heart, whilst in regard to the toxic doses it is more than probable that they directly depress the heart.

Arduin, Demme, Lepine, and Armand all affirm that in the poisoned frog the heart is arrested in diastole, but Coppola states that antipyrin has no influence upon the circulation in the frog, that in many cases after the largest dose the heart is arrested in systole, and that in the Williams apparatus no effect is produced by antipyrin upon the isolated heart unless the dose be enormous. Faval[24] found, however, that while moderate doses have little effect, large doses diminish the frequency and force of the cardiac contractions in the isolated heart of the frog, and finally cause diastolic arrest.

The action of the drug upon the vaso-motor system is at present writing very doubtful. Cerna and Carter affirm that it has no influence upon the blood-vessels, but give no proof of this; and the fact ascertained by Casimir, that the rise of arterial pressure is accompanied by a

distinct decrease in the size of such vascular internal organs as the kidneys, indicates that the drug produces a vaso-motor spasm, a view which receives confirmation from the assertion of Arduin, that antipyrin is a powerful local hæmostatic. On the other hand, Querrolo (quoted by Armand), employing the plessimograph of Mosso, found that the arm is increased in size under the influence of antipyrin, and therefore that the peripheral vessels are dilated, and Casinfir affirms that similar dilatation can be seen in the blood-vessels of the ears of rabbits poisoned by antipyrin.

The fall of the arterial pressure is without doubt, at least in part, the result of a depressing influence of the drug upon the heart itself; but if the observation of Bettelheim (quoted by A. Biach[25]), that during the fall of blood-pressure the temperature of the interior of the body notably falls, while that of the exterior correspondingly rises, be correct, vaso-motor paralysis probably is also a factor.

According to the researches of Cerna and Carter, the pulse is usually increased in rate by full doses of antipyrin through a paralytic influence upon the inhibitory nerves, but afterwards becomes decreased in number through the direct action of the drug upon the heart itself.

The peculiar lividity often seen in persons under the influence of antipyrin is probably due to changes in the blood itself. According to Lepine, methæmoglobin is largely formed during the poisoning, but Crolas and Hagoumeng[26] failed to detect it. The three observers are in accord in finding that the number of the red corpuscles is not perceptibly affected, even by the continuous exhibition of very large doses.

Temperature.—When given in large doses to the normal animal, antipyrin frequently, but not invariably, produces fall in the bodily temperature; in the fevered animal this fall is more marked and more constant. Its cause is not entirely established, but it is probably the result of an influence exerted directly upon the thermogenetic centres. It is certainly independent of any action upon the general circulation, as we have seen the temperature of fevered dogs reduced four or five degrees by antipyrin without change in the arterial pressure.

In seven out of nine experiments made by H. C. Wood, E. T. Reichert, and Hobart A. Hare*[27] upon normal animals, there was a decrease in both the production and the dissipation of animal heat. In two experiments both functions were distinctly increased. When tetanic convulsions occur from antipyrin there is a marked rise of the bodily temperature. In both of the calorimetric experiments in which the heat-production was increased, very large doses of antipyrin had been given, and it is believed that the animal suffered convulsions in the calorimeter. In almost

* The course of fever produced by injections of pepsin in the blood varies, and in calorimetric experiments it is not sufficient to give pepsin and when the temperature has risen administer the antipyretic and study calorimetrically the result. The best way is to produce a paroxysm of fever on one day and study it calorimetrically through its whole course; some days subsequently, the same animal and dose of pepsin being used, the course of the fever is to be modified by the antipyretic, and the heat-dissipation and heat-production of the two days contrasted.

all the experiments the decrease of heat-production was very much greater than the decrease of heat-dissipation : it would appear, therefore, that antipyrin in the normal dog primarily lessens heat-production, the reduction of the heat-dissipation probably being the result, at least in part, of the lessened heat-production. In experiments upon dogs in which fever had been produced by injections of pepsin, both heat-production and heat-dissipation were markedly decreased, but usually heat-production was more affected than was heat-dissipation.

The experiments of Destrée[28] and of Engel (quoted by Biach) are, so far as they go, in accord with those just given, whilst Cerna and Carter found pronounced decrease of heat-production with simultaneous increase of heat-dissipation in dogs fevered by injections of putrid blood ; so that it would appear that *antipyrin reduces temperature in fever by decreasing the heat-production.** That antipyrin acts through the nervous system is strongly indicated by the influence which it has over fever produced by nerve-lesions.

P. J. Martin,[29] R. Gottlieb,[30] and H. Girard[31] are in accord in finding that the rise of temperature which is produced in the rabbit by punctures in the neighborhood of the striate body is lessened or altogether put aside by antipyrin. Martin has further found that heat-production is also lessened under these circumstances. Gottlieb[32] states that Sawadowski has determined that, in the dog whose spinal cord is cut high up, antipyrin no longer reduces the temperature.

The studies which have been made by chemists as to the effects of antipyrin upon the elimination of waste products, taken as a whole, are in accord with the view that antipyrin lessens heat-production. It is indeed true that Chittenden and Cummins[33] were unable to find that antipyrin, either in large or in toxic doses, has any effect upon the elimination of carbonic acid by the animal ; but before these results can be considered as established further experimentation is necessary. Again, Armand thought that he had chemically proved that antipyrin increases the elimination of urea ; but the original studies of Umbach,[34] who found that large doses of antipyrin very markedly decrease the elimination of urea, have been so abundantly confirmed † that it would seem that it must be

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* The experiments of Gottlieb, however, are not consonant with this view ; in three experiments hypodermic injections of antipyrin were followed by increased heat-production, with a greater increase of heat-dissipation and consequent fall of temperature. Similar results were also reached in rabbits in which fever had been produced by pricking nerve-centres (*Archiv f. Exper. Path. u. Pharm.*, 1891, xxviii.). These experiments are certainly open to the objection that it is not shown that the changes in heat-dissipation and production which were noted were really produced by the antipyrin, and were not due to the confinement in the calorimeter or to the natural variations in the course of the fever itself ; in other words, there were no proper control experiments.

† Among the chemists who have reached this conclusion by practical experimentation may be mentioned Wiczkowski (quoted by Umbach), Walter, of St. Petersburg (*Therap. Gaz.*, ii.), F. Müller (*Jahresb. für Thierchemie*, xiv.), Ries (quoted by Biach), Albert Robin (*Bull. Acad. Méd.*, 1887, xviii.), and Jacubovitsch (*Brit. Med. Journ.*, 1888, ii.). Tausk's (*Schmidt's Jahrb.*, ccxxxvi.) failure to get a pronounced effect may have been due to his having used too small doses.

considered established that antipyrin, *both in health and in fever, diminishes the output of the nitrogenous products of tissue-waste.**

Antiseptic Influence.—The influence of antipyrin upon pathogenic micro-organisms and upon fermentation has been elaborately studied by Engel (quoted by Biach), who found that such influence is so exceedingly feeble as to have for practical purposes no existence. On the other hand, Chittenden and Stewart state that antipyrin inhibits, and if present to the amount of three per cent. stops, the digestive action of the acidulated pepsin solution, whilst Cazeneuve and Visbeck [35] find that one per cent. of antipyrin is sufficient to indefinitely put off putrefaction of the blood. They also confirm the fact that antipyrin is capable of inhibiting the action of ferments like pepsin and diastase. Roux and Rodet [36] find that a four per cent. solution is sufficient to very sensibly affect the *Bacillus coli communis.*

SUMMARY.—Antipyrin is absorbed rapidly, and eliminated rapidly, at least in part, unchanged. Whilst the ordinary dose of antipyrin produces no distinct symptoms, when in large enough amount the drug causes languor, malaise, cyanosis, depression of the circulation, giddiness, somnolence, epileptiform convulsions, a measle-like exanthema, coma, and collapse. Owing to idiosyncrasy, it provokes in some cases violent urticaria and subdermal inflammation, which may be accompanied by fever and other constitutional disturbances. It is probably a primary stimulant and a secondary depressant of the motor spinal cord. It is certainly a paralyzant to both the motor and sensory nerve-trunks, and seems to have also some action upon the muscles themselves. A small dose may moderately increase arterial pressure, probably by directly stimulating the heart and the blood-vessels, although upon these points we have no certain knowledge. The final fall of arterial pressure is due, at least in part, to a direct action upon the heart. In sufficient amount antipyrin causes methæmoglobin to appear in the blood. It increases the respiratory rate by a centric action. It probably lessens the production of animal heat by a direct action through the nervous system, independent of any influence upon the circulation, and appears also to stimulate heat-dissipation. Both in health and in fever it diminishes the output of the nitrogenous products of tissue-waste.

THERAPEUTIC ACTION.—In fever cases, about half an hour to an hour after the ingestion of a full antipyretic dose of antipyrin profuse sweating occurs, and is soon followed by a fall of temperature, which is, however, independent of the diaphoresis.

According to Carl von Noorden,[37] the sweating can be arrested by the use of hypodermic injections of atropine or agaricin without affecting the fall of temperature. Moreover, the sweating is not invariably present, and in dogs, which practically do not sweat, antipyrin is a powerful antipyretic in fever.

* It would further appear probable that antipyrin alters the normal relation between the various excrementitious substances, since Umbach has found that while the urea was markedly diminished, uric acid was scarcely altered; and Robin affirms that in his experiments the elimination of uric acid was even augmented.

According to most authorities, the depression of temperature lasts longer than that caused by some other antipyretics, continuing from two to ten hours. It is accompanied by a reduction of the rate but not usually of the force of the pulse. In some cases the sweating is not profuse, and it is probably under such circumstances that observers have noticed a markedly increased diuresis. Usually the patient is more comfortable under the action of the drug than at other times ; sometimes, however, there is distressing vomiting.

Antipyrin may be employed as an antipyretic in almost any disease accompanied by high temperature, such as *pneumonia*, *erysipelas*, and *typhus*, *scarlet*, *yellow*, and *typhoid fevers*, *rheumatism*, etc.; it has also been freely given in the hectic fever of *phthisis*, but various observers state that in such cases it produces so much feebleness and general depression as to forbid its use : nevertheless, our own observation is that when used with caution it often gives great relief. In *typhus fever* it reduces the temperature, but in a number of recorded cases it has induced very serious collapse. It appears to have some specific action in rheumatism, but does not in this respect equal salicylic acid. According to A. Pribram,[38] in *pneumonia* the frequency of the respiration is distinctly lessened by it, but this is probably due simply to the lowering of the bodily temperature. In children it has been used with asserted good results by a number of clinicians, and it appears to be especially useful in the pneumonia and bronchitis of the young.

The second indication for the meeting of which antipyrin is sometimes used with success is the *relief of motor disturbance*. Over the minor spasmodic conditions of *hysterical* origin, over *chorea*, etc., antipyrin has a certain amount of power. In 1888 Sonnenberger[39] commended it very highly in *whooping-cough*, stating that if given at regular intervals it greatly lessens the number of paroxysms, or even aborts the disease ; and further clinical experience seems to show that the drug has real value. M. A. Chouppe states that antipyrin has great power in relieving uterine pains after parturition or in *dysmenorrhœa*, and that if it be given during labor along with ergot it allows the contractions to go on, but renders them painless. In more severe spasmodic disorders antipyrin sometimes does good. It is certainly worthy of trial in *tetanus*, especially when the temperature is high. It may be given in *epilepsy* with some hope of success, since its influence in preventing the return of convulsions is sometimes extraordinary, although in the great majority of cases it fails entirely. We have studied it in a large number of cases, but are unable to point out any indications which will warrant in an individual case an *a priori* opinion that antipyrin will do good. The only method is that of trial. Not less than forty grains a day should be given, and if, after a time, no cyanosis or muscular weakness mark the physiological action of the drug, and the convulsions still recur, the dose should be increased up to the physiological limit. The combination of antipyrin with ammonium bromide affords much better results than either

drug alone, and it has become with us a routine practice to prescribe in epilepsy a mixture of ammonium and strontium bromide with antipyrin. We have given to a large number of cases fifteen grains daily of the antipyrin in this combination for many months, and even for years, without cumulative action or perceptible effect upon the general nutrition or the general nerve functions, except that in some cases, probably by disturbance of thermogenesis, a condition of such intolerance of cold is produced that the drug has to be withdrawn, at least for a time. Antipyrin has been used with alleged success in *laryngismus stridulus*, in *nocturnal emissions*, in *asthma*, and in *urinary incontinence* of children.

The third indication which may sometimes be advantageously met by antipyrin is the *relief of pain*. In April, 1887, Sée announced to the French Academy of Medicine that antipyrin is a powerful analgesic, which when given in doses of from forty-five to ninety grains a day will control almost all forms of pain. Such doses, however, border upon toxic, and are rarely justifiable. Moreover, they are scarcely ever necessary in properly selected cases. Abundant clinical experience has shown that antipyrin for the relief of ordinary inflammatory pains is not reliable, and is in every respect inferior to opium; but that it is a very valuable agent against various nervous pains, sometimes giving much more relief than does opium, and usually causing less disturbance to the system. Especially is it effective in *rheumatic pains* and in *migraine* and other forms of *neuralgia* in which the pain is the outcome of nerve-storm; it will, indeed, often control the pangs of *locomotor ataxia;* we have even seen it abort a *gastric crisis*. Whether it acts by a true analgesic influence, or whether it simply puts aside the nerve-storm which is the cause of the pain, is entirely unknown. In violent *hemicrania* sleep follows relief; but antipyrin is not a true hypnotic. Antipyrin is stated greatly to increase the analgesic effects of morphine, and is itself, in headache at least, made much more effective by caffeine.

Antipyrin has also been used in various disorders not included under the indications already given, often without sufficient reason.

M. H. Feeny[40] reports *subacute Bright's disease* cured by it; Clement,[41] that it is of value in bringing about absorption of *pleuritic effusions*. Both in *diabetes mellitus* and *diabetes insipidus* it has been used with asserted good results. Saint-Phillippe[42] commends it highly in *infantile diarrhœa* with indigestion and pain. Salemi affirms that it is an active and practical *antigalactagogue*, and in this has been confirmed by Ryan-Tennison and by Guibert.[43]

ADMINISTRATION.—Antipyrin may be administered hypodermically, by the mouth, or by the rectum. The dose for a child of one or two years of age may be set down as two to three grains (0.13–0.2 Gm.); for a child five years old, three to seven grains (0.2–0.46 Gm.); for the adult the dose should not exceed twenty grains (1.3 Gm.), and ten grains (0.6 Gm.) are usually sufficient, in fever cases, repeated every one or two hours until forty grains are given, or sweating comes on, or the tem-

perature falls. In children it would not be safe to repeat the dose more than once. Some authorities prefer a single large dose of from forty to sixty grains (2.5–4 Gm.) in the adult.

Hypodermic Use.—Antipyrin has been used to a considerable extent hypodermically for the relief of pain, and in neuralgias and nerve-pains good can sometimes be achieved by its local influence. The burning pain produced by the injection of a thirty per cent. solution usually lasts only a few minutes, and is not followed by local inflammation. Verneuil,[44] however, has reported partial gangrene of the foot following and apparently produced by a hypodermic injection of antipyrin for the relief of sciatic neuritis.

Toxicology.—In describing the action of antipyrin upon the normal human organism, sufficient has been said in regard to the general symptoms produced by poisonous doses. It seems necessary, however, to point out that these symptoms in a large proportion of recorded cases seem to have been due to constitutional peculiarities of the individual rather than to the use of very large doses of antipyrin, and they are rarely, if ever, attended by any danger to life. Thus, E. W. Young[45] reports a serious poisoning by six grains of antipyrin. Theo. Schwabe[46] reports a case in which fifteen grains of antipyrin, given to a young woman for neuralgia, produced violent poisoning with collapse, complete amaurosis, cyanosis, urticaria, etc. Almost equally inexplicable are those cases which have especially occurred in typhoid and other fevers, in which fatal depression has been produced by doses of antipyrin that were not larger than have frequently been used without evil results. Thus, in Barrs's[47] case, thirty-five grains of antipyrin were given to a puerperal woman with a temperature of 103.6° F., and followed in three hours by half the quantity, after which the temperature sank to 98° F., and, in spite of stimulation, death occurred thirty-two hours later. Our knowledge of the physiological action of antipyrin seems to negative the supposition that the depression in these fever cases is due to any direct action upon the heart or other vital organ. Heat is a stimulant to function, and it may be that the cause of the collapse is the sudden fall of bodily temperature in a person whose nervous system is excessively enfeebled by a fever of typhoid nature.

ACETANILIDUM—ACETANILID. U.S.

Antifebrin, or *phenylacetamide*, is an aniline in which one atom of hydrogen has been replaced by the radical acetyl; or it may be considered as an ammonia in which one atom of hydrogen is replaced by phenol and another atom by acetyl. It is a white, crystalline substance, entirely without odor, having a bitter, mildly piquant taste. It is soluble, at 59° F., in one hundred and ninety-four parts of water and in five parts of alcohol.

Physiological Action.—*Local Action.*—According to the experi-

ments of L. Frothingham and J. H. Pratt,[1] acetanilid is distinctly antagonistic to disease germs, scarcely killing them, but markedly inhibiting their growth. Applied in the form of powder to a wound or mucous membrane, it acts as a stimulant or feeble irritant, a desiccant, and probably also as an analgesic.

Absorption and Elimination.—Absorbed into the blood by some unknown method, acetanilid is in great part or altogether converted into the paramidophenol sulphate,* and as such escapes from the kidney. It is probable that it breaks up in the organism into acetic acid and aniline, and that the aniline is then oxidized into paramidophenol, which unites with sulphuric acid.†

Cahn and Hepp,[2] however, affirm that antifebrin escapes finally with the urine in great part unaltered, and that only a small portion of it is converted into aniline and acetic acid; but Müller as well as Pavai Vajna[3] and Kumagawa[4] state that antifebrin cannot be found in the urine, and consequently that it undergoes entire decomposition. Jaffe and Hilbert[5] found that in dogs acetanilid passes off chiefly as o-oxycarbonol and as paramidophenol, both united with glyco-uronic and sulphuric acids; in rabbits, chiefly as paramidophenol, paired with the acids. It is probable that the proportion of antifebrin which is decomposed varies with the size of the dose and the condition of the system.

The medical virtues of antifebrin were first discovered by Cahn and Hepp, and have been abundantly confirmed by numerous observers. When given to healthy men in doses of seven to ten grains it usually produces no appreciable effect. The repetition of this dose may cause somnolence, constipation, occasionally headache or nausea, malaise, and a peculiar cyanotic condition of the face and extremities. When given to persons suffering from fever in doses of ten grains antifebrin usually produces in about an hour fall of temperature, which reaches its maximum in two or three hours and may continue from six to seven hours. In some cases at this time the cyanosis is apparent; usually, but not always, the fall of temperature is accompanied by a profuse sweating, which is generally described by clinicians as being less than that produced by corresponding doses of antipyrin. The fall of temperature is not dependent upon sweating, since it sometimes occurs without the sweating, and G. Pavai Vajna finds that the sweating can be arrested in great part by atropine without interfering with the thermic action of the drug. In

* In an elaborate research on various drugs of the aniline group (*Deutsch. Med. Wochensch.*, 1895, xxi.) it was found that those substances which produced in the organism *paramidophenol* or *paracetamidophenol* were active, whilst those which made *ethyl-acetamidophenol* were not active.

† The changes which occur in antifebrin in the system have led to the theory that its medical virtues are dependent upon the liberation of aniline in the blood. The symptoms produced by antifebrin are certainly similar to those caused by aniline. Thus, Hercel states that in a case of aniline-poisoning the symptoms were colossal cyanosis, sweating, vomiting, tinnitus aurium, dyspnœa, fixedness of pupils, disturbance of sensibility, and a temperature-fall of 5.3° C., accompanied by a marked decrease in the coloring-matter of the blood and of the number of red blood-corpuscles.

rare cases the lowering of the bodily temperature has been coincident with the occurrence of collapse. Occasionally there is an eruption somewhat similar to that commonly produced by antipyrin, which is especially abundant upon the face and forehead, and of a dark red color. Sometimes the eruption resembles that of scarlatina, and there may be much subdermal swelling (Armin Hugher[6]).* Mydriasis and deafness, with ringing in the ears, have been noted occasionally. Collapse appears to be less frequent than with antipyrin. The experiments of Hobart A. Hare[7] show that at present inexplicable cardiac failure may occur suddenly.

In the experiments of Herczel,[8] the symptoms produced by fifteen to twenty grains in rabbits were loss of the reflexes, tremors deepening into periodic convulsive movements, great fall of temperature, frequent, irregular, superficial respiration, retention of urine, coma, and general paralysis, ending, if the dose had been large enough, in death, which could not be prevented by artificial respiration. The heart was arrested in diastole. After the prolonged action of the drug there was fatty degeneration of the heart, liver, and kidneys. Weill[9] noticed, in addition to these symptoms, an anæsthesia, which in the later stages of the poisoning was almost complete.

Nervous System.—The cause of the convulsions of acetanilid-poisoning does not seem to have been determined. The coma which is present in the advanced stages of the poisoning indicates that, directly or indirectly, antifebrin affects the cerebral function, but consciousness is stated by experimenters to be preserved at a time when the lower portion of the nervous apparatus is distinctly affected. According to Bokai,[10] antifebrin *paralyzes motor nerve-endings* of the frog's muscles in a manner similar to curare, and when brought in contact with the *muscle* itself for a sufficient length of time destroys its capability of contraction. In the poisoned animal, however, just before death the muscles respond actively, although irritation of motor nerve-trunks fails to elicit response.

Circulation.—Usually when antifebrin is given to patients with fever there is a fall in the pulse-rate corresponding to the fall of temperature. The size of the pulse is also reduced, and it may even become thready. Weill has found that, injected into the frog, the drug causes at first an acceleration of the heart's beat, with apparent increase in the force of the impulses, followed after a time by slowing and irregularity of contraction. In the earlier stage the size of the pulse-wave is increased and the respiratory curve is more accentuated ; later the pulse-oscillations diminish and become irregular and quickened, and if the dose has been large enough the manometric writing resembles that produced by asphyxia. In the earlier stages of the action there is a slight rise in arterial pressure.

The cyanosis of antifebrin-poisoning has been thought to be due to the formation of methæmoglobin, but in a case of violent poisoning with excessive cyanosis, Freund[11] was unable to detect anything abnormal in the blood by microscopical or spectroscopical examination. Herczel

* See also *Medical News*, lxxii. 791.

states that the red corpuscles do not adhere in rouleaux, that they are somewhat granular, and that, when the drug is given to dogs for a length of time, the blood is less alkaline than normal, and contains in its serum dissolved coloring-matter. According to Lepine and Aubert,[12] the oxygen of the blood is distinctly decreased.

Nutrition.—Kumagawa found that while small doses had no definite effect, large doses enormously increased the nitrogenous elimination ; but in Lepine's experiments the results varied, there being sometimes an increase and sometimes a diminution, while H. C. Taylor[13] obtained a slight increase : so that it is impossible at present to say what is the action of the drug upon protoplasmic chemical activity.

According to Kumagawa, antifebrin exerts a strong antiseptic influence upon intestinal changes, decreasing the bacteria in the intestines, and the urinary indican.

Temperature.—The only information we have concerning the method by which acetanilid lowers bodily temperature is furnished by the experiments of H. A. Hare and E. M. Evans.[14] It is not sufficient for a positive conclusion, but indicates that in fevered animals *antifebrin produces a fall of the temperature by decreasing heat-production.*

In fifteen experiments upon normal animals, which in nearly all cases were allowed to run free, Hare obtained a distinct fall of temperature from antifebrin,—a result confirmed by Evans, but not in accord with the results of Cahn and Hepp, who found that antifebrin had not a constant influence upon the temperature of the normal animal. Hare, employing the calorimeter of H. C. Wood, found that in the normal animal heat-dissipation and heat-production were variously affected, in some cases being notably increased, in other cases notably decreased, and in others not distinctly altered. Evans, employing the D'Arsonval calorimeter, also reached various results. In eleven experiments heat-dissipation was decreased nine times, while heat-production was increased four times and decreased five times. In examining the records of the calorimetric experiments made by Hare and Evans on the normal animal, we find that not only did the rectal temperature *not fall* under the influence of antifebrin, but in nearly every instance there was a very distinct rise, amounting in some cases to over a degree. It is evident, therefore, that these experiments cannot be used to explain how antifebrin reduces temperature when it does cause a fall. The attempt to reason how a certain result is produced by a remedy from experiments in which that result was not produced is necessarily futile.

In Hare's experiments made upon dogs in which fever was caused by the injection of pepsin, antifebrin failed to produce any constant fall of the bodily temperature, probably because the dose was not large enough. In the calorimetric studies heat-production was usually decreased, but sometimes it was increased,—an assertion which is also true of heat-dissipation. These experiments must likewise be laid aside, because there was no fall of temperature caused by the antifebrin. In Evans's experiments with fever produced by the injection of albumose, the antifebrin nearly always caused a distinct reduction of temperature. In the calorimetric studies the results obtained were constant, there being in each of the six consecutive experiments a decrease in both the hourly heat-dissipation and the hourly heat-production, the amount of decrease seemingly bearing some relation to the fall of temperature. It is plain that a decrease of heat-dissipation would have a natural tendency to elevate bodily temperature, and therefore the fall of temperature must have been due

to the decrease of the production, which in turn gave rise to the decrease in the heat-dissipation.

THERAPEUTICS.—The medical application of antifebrin appears to be exactly parallel to that of antipyrin. There is some reason for believing that it is less apt than is antipyrin to produce collapse, or painful eruptions upon the surface, or other disagreeable effects. This may, however, simply be because it has been less freely used than antipyrin, since it is certainly capable of having any of these actions.

Thus, Quast (quoted by Biach) reports a case in which cyanosis, collapse, and death were produced by it in a child; Marichaux [15] one in which four grains caused in a child five months old intense cyanosis, fixed pupils, coldness of extremities, rapid, almost imperceptible pulse, very superficial breathing, great sweating, and complete unconsciousness, with final recovery. Doll (quoted by Biach) gives a case in which about a drachm produced in a woman vomiting, cold sweat, intense prostration, great coldness of the extremities, dilated pupils, and rapid irregular heart-action, without complete loss of consciousness. According to Sembritzki,[16] the drug acts very badly on pregnant and nursing women.

Antifebrin may be substituted for antipyrin for the reduction of temperature in fever, for the relief of pain, and for the prevention of epileptiform attacks. According to Lepine,[17] it will relieve not only the fulgurant pains of spinal disease, but also the tremors produced by *multiple sclerosis*, and is often useful in *epilepsy*. Dose, five to fifteen grains (0.3–1 Gm.).

Acetanilid affords a useful surgical dressing, and has the superiority over iodoform of being free from odor, and perhaps of being more analgesic. It is frequently employed with equal amounts of boric acid, finely powdered, in the treatment of minor infected wounds. The powder may be freely used, or an ointment of from ten to forty per cent. strength; in *vaginitis* or *urethritis* a mixture (twenty to forty grains to one fluid-ounce) with gum-arabic water may be injected. The free external use is not entirely devoid of danger, as cases have been reported of collapse with intense cyanosis and subnormal temperature produced by the surgical use of the drug.*

PHENACETIN.

Phenacetin, or *Acetphenetidin*, an acetyl derivative of amidophenol, crystallizes in tasteless, colorless needles, slightly soluble in water, more so in alcohol. Phenacetin is eliminated by the kidneys, probably entirely altered, phenetidin appearing in the urine. According to Müller,[1] this change must take place after absorption, since both the gastric and pancreatic secretions are without effect on the compound. O. Hinsberg and A. Kast [2] have found that when given to dogs in doses of fifteen-hun-

* See *Phila. Polyclinic*, 1897; *Atlantic Med. Weekly*, 1898; and *Medical and Surgical Rep.*, 1897, lxxvi.

[illegible] two-tenths of a gramme per kilo phenacetin has no effect, but [illegible] large doses it causes vomiting, irregular gait, hurried respiration, and somnolence, followed by general cyanosis and discoloration of the blood, due to the formation of methæmoglobin.

The therapeutic dose of phenacetin produces no symptoms, but the toxic dose is said to cause violent vomiting, great cyanosis, chocolate-colored urine, yellow discoloration of the body, leucocytosis, and death (Krönig). Mahnert[3] states that the muscular weakness produced by phenacetin is of spinal origin, and that in massive doses the drug is antagonistic to strychnine; also that both respiration and heart are paralyzed by it. According to the same observer, it is chiefly eliminated unchanged; and the urine gives a positive Trommer's reaction, although containing no sugar. Ledoux[4] asserts that in doses of 0.5 gramme per kilo phenacetin causes a fall of the blood-pressure; but as he used an alcoholic solution, his results are not entirely reliable. In some experiments, as yet unpublished, done in the pharmacodynamical laboratory of the University of Pennsylvania by Harold B. Wood, the drug, given intravenously suspended in water, had absolutely no effect on blood-pressure. Doses of 0.5 gramme per kilo killed by arrest of respiration; which can perhaps, however, be attributed to the mechanical influence of undissolved particles. Frogs allowed to swim in a saturated aqueous solution of phenacetin in four hours became totally paralyzed, the motor nerves and muscles retaining their irritability. Ott[5] found that phenacetin pronouncedly decreases heat-production without producing distinct alteration of blood-pressure, and, therefore, probably acts as an antipyretic by lessening the heat-production through an influence upon the nervous system.

THERAPEUTICS.—Phenacetin has been largely used as an antipyretic, and for the relief of pains of such character as antipyrin is employed against. Large amounts of it can apparently be taken without serious result. In a case reported to us by E. C. Wagner, one hundred and twenty grains were taken in twelve hours without the production of any symptoms. The only serious case of poisoning by it that we know of is that recorded by Hollopeter,[6] in which a woman took twenty-two and a half grains in six hours, producing collapse, with marked lividity, great dyspnœa and restlessness, cold perspiration, and slightly dilated pupils, ending in recovery.

There can be no doubt of the efficiency of phenacetin, and it would appear that it more rarely produces unpleasant symptoms than antipyrin, though urticaria has been noticed after its exhibition (Mahnert). If the statements of Crombie[7] and of Hirschfelder[8]—that it acts more gradually than other antipyretics, and that its influence does not reach its maximum for three or four hours—be correct, phenacetin is probably the most valuable of the antipyretics, especially as it seems to be the least poisonous. At present it is probably the most used of its class. Dose, from ten to twenty grains (0.65–1.3 Gm.). Phenacetin is highly commended by M. H. Lee[9] as a local antiseptic dressing.

PHENOCOLL HYDROCHLORIDE.—Phenocoll occurs in white needle-like crystals ; it is made by the action of glycocoll upon phenetidin. Its hydrochloride is a white, finely crystalline powder, very soluble in water.

PHYSIOLOGICAL ACTION.—The action of phenocoll upon the animal organism is not very marked, Von Mering having found that twenty-three grains of it will not produce any pronounced symptoms in the rabbit. When given, however, in sufficient quantity it is certainly capable of disturbing the whole economy, although its physiological action has not been worked out. According to Isaac Ott, the toxic dose produces, in the frog, paralysis of both the motor and sensory functions of the spinal cord, with death from diastolic arrest of the heart ; in rabbits, quietude, partial paraplegia, and cyanosis, with acceleration of the respiratory movement and depression of temperature and of the arterial pressure. David Cerna and William S. Carter determined that the influence of phenocoll upon the circulation is exceedingly feeble. The fall of the arterial pressure caused by enormous doses occurred after section of the spinal cord and the pneumogastrics ; so that it must be concluded that phenocoll, when in sufficient amount, is a cardiac depressant. The action of smaller doses was not made out. The pulse was found by Cerna and Carter to be primarily decreased by inhibitory stimulation, then increased by inhibitory paralysis, and finally diminished by direct action upon the heart.

The same investigators affirm that phenocoll has no action upon the blood, but the correctness of this seems to be challenged by the cyanosis which has been noted both in man and in rabbits. In experiments made upon animals with fever, Cerna and Carter found that the fall of temperature produced by phenocoll is due to an enormous reduction of heat-production, heat-dissipation not being practically altered. As the result of some evidently not very elaborate chemical studies, P. Balzer[1] states that phenocoll very distinctly increases the nitrogenous elimination : the correctness of this is very doubtful.

Phenocoll is rapidly absorbed and almost as rapidly eliminated. According to Cohnheim, it may be detected in the urine from one to nine hours after its ingestion. It is probably in part oxidized in the system, since the urine after its free administration becomes of a dark, reddish-brown color. It is possible, however, that this color is due to indican and biliary substances, both of which have been found in the urine.

THERAPEUTICS.—In 1891 Hertel and Herzog[2] stated that phenocoll rarely, if ever, produces gastro-intestinal irritation or other disagreeable symptoms, that its antipyretic action is quick and never accompanied by any depression, and that the free sweating which is apt to occur with it may readily be prevented by minute doses of atropine. Both Hertel and Herzog assert that phenocoll is a valuable remedy in *acute* and *chronic rheumatism*. The first reports regarding the antipyretic action of the drug have received wide confirmation, and it would seem that phenocoll is one of the safest, promptest, and most efficient members of its class.

On the other hand, it has been stated that in rheumatism and as an analgesic in ataxic or other nerve pains it is inferior to the older remedies. These results may, however, have been due to a too timid use of the phenocoll, as it is affirmed by some clinicians that five grammes or seventy-seven grains of it are usually required to have an effect in rheumatism, whilst most writers give the dose as much smaller than this. In rare instances it produces vomiting, but we have met with no cases of human poisoning by it. The ordinary dose may be set down as twelve to fifteen grains (0.78–1 Gm.), in solution or capsule.

EXALGINE.—*Methylacetanilid* occurs in needles or long tablet-like crystals, barely soluble in cold water, freely soluble in hot water. When given to man in full, non-poisonous doses, it produces some slight amblyopia and vertigo, accompanied in some patients by vomiting, tinnitus aurium, headache, drowsiness, and vaso-motor disturbances, such as sweating. After large doses cyanosis is pronounced, but no eruption upon the surface of the skin seems as yet to have been noticed. No fatal poisoning by it has been reported, but in a case of A. C. Hartley's eighteen grains in divided doses produced a general motor paralysis, with dyspnœa, intense pallor, dilated pupils, and pronounced palpitation of the heart. In a second case, two doses of three grains each produced in a boy fourteen years old a sudden almost lethal heart-failure, with dilated pupils and dyspnœa. In a case reported by Gillespie there were violent convulsions.*

According to Brigonnet, hypodermic injections of exalgine cause in the lower animals violent epileptiform convulsions, profuse salivation, cyanosis, disturbance of breathing, fall of temperature, and alteration of the blood, which becomes dark prune-colored and contains an abundance of methæmoglobin. The muscles at the seat of the injection are said to be locally paralyzed, and although small doses increase slightly the blood-pressure, after the toxic dose the pressure suddenly falls. The urine does not become albuminous nor bloody.

Exalgine has been used as an antipyretic, but to a very much larger extent as an analgesic, and is said also to be useful in *chorea* and *polyuria*. According to Moncorvo, as an analgesic it has at least five times the power of antipyrin. Dose, three to six grains (0.2–0.4 Gm.), not more than twelve grains being exhibited in the twenty-four hours. Moncorvo gives the dose for a child five years old as one and a half grains (0.09 Gm.).

SALIPYRIN.—*Antipyrin Salicylate* is a white, coarsely crystalline, odorless, slightly sweetish powder, readily soluble in alcohol. It is commended by Guttmann and Kollmann as an active antipyretic and antirheumatic, which rarely produces toxic symptoms, although an eruption resembling that of antipyrin has been noted; the color of the urine is not affected, but tests show the presence of salicylates. Kollmann states that it sometimes vomits, and that the daily dose should never exceed forty-

* See also *Bull. de Thérap.*, March, 1891; and *Brit. Med. Journ.*, Feb. 1890.

five grains (2.9 Gm.), and should always be less than this in the beginning, as some individuals are intolerant of it. Salipyrin has been used to a considerable extent in all forms of *rheumatism*, in *influenza*, in various fevers, in *migraine*, and in the whole class of diseases in which its component constituents have been found to be useful; also locally in *coryza*. The usual dose is from seven to fifteen grains (0.45–1 Gm.), in capsule or tablet, repeated every three or four hours, but some clinicians prefer a single large dose of forty-five grains (2.9 Gm.).

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CLASS II.—LOCAL REMEDIES.

FAMILY I.—STOMACHICS.

STOMACHICS are drugs which especially affect the mucous membrane and other coats of the gastro-intestinal tract so as to increase functional activity. A *simple bitter* is a substance of vegetable origin and of a bitter taste, which has no influence upon the general system, but markedly affects the stomach as a stimulant. Simple bitters probably influence not only the peptic glands but also the muscular fibres, since Paul Terray[1] found that the movements of the excised stomachs of dogs, kept in a warm salt solution, were increased in the order of naming by extract of gentian, cetrarin, condurangin, extract of taraxacum, quinine, and extract of quassia. Cetrarin was remarkable for its influence upon the intestinal movements. Although simple bitters may, by increasing the amount of food taken, affect the general nutrition of the body, they are essentially locally acting drugs. Probably all bitter vegetable substances are stimulants to the gastric mucous membrane, but in many of them, as in morphine and strychnine, such power is completely overshadowed by other inherent properties. Some of these active bitter vegetable substances are indeed employed on account of their influence upon the alimentary tract, notably quinine and strychnine, but in others of them, like morphine, the local is entirely swallowed up in the general influence. By virtue of their stimulant power the simple bitters produce, when in overdoses, nausea, and may even cause active irritation of the gastro-mucous membrane. They have also some tendency to act upon the bowels. They are essentially irritant, and are contra-indicated by inflammation or over-sensitiveness of the alimentary mucous membrane. They are especially indicated by loss of appetite, when such loss of appetite is the outcome of a depressed condition of the stomach, but when it is the result of gastro-inflammation they will do harm. A second class of stomachics are the so-called *aromatics*, which depend for their activity upon the presence of a volatile oil. They differ from the simple bitters in being more powerful but less permanent as local stimulants. (See page 613.) A third class of drugs contain both volatile oil and bitter principle, and unite the properties of the aromatics with those of the simple bitters. These are the so-called *aromatic bitters*.

SIMPLE BITTERS.

QUASSIA. U.S.

The wood of Picræna excelsa, a large tree, native of Jamaica. This wood is light both in density and color, somewhat resembling that of the tulip-tree, but distinguished by its intensely bitter taste. It is kept in the shops in billets and in raspings. The active principle is *Quassin*, an intensely bitter, neutral, crystalline principle. *Simaruba*, the bark of the root of Simaruba officinalis, also contains quassin, and may be substituted for quassia.

PHYSIOLOGICAL ACTION.—Quassia can hardly be said to be poisonous to man, the largest doses producing in the adult only gastric irritation, but F. Venn[2] has reported a case in which in a young child the injection into the rectum of a decoction representing two ounces of quassia was followed almost immediately by vomiting, stupor, relaxation, and collapse, ending in death. According to I. Hoppe,[3] *quassin*, when given to frogs in doses of one grain, will produce weakness, convulsions, respiratory and cardiac failure, ending in death. Locally, quassin is a distinct irritant. In man, five milligrammes of the pure crystalline form notably increased the secretion of bile and of urine, and caused some looseness of the bowels and stimulation of the bladder ; whilst fifteen milligrammes produced violent frontal headache, burning pains in the œsophagus and throat, nausea, vomiting, vertigo, excessive nervous restlessness, diarrhœa, and very frequent micturition, but diminished renal secretion.[4]

THERAPEUTICS.—Quassia is probably the most active of all the simple bitters, and may be used whenever such remedies are indicated. In cases of *seat-worms* in children, a strong infusion of quassia (two ounces to one pint) affords a most harmless and efficient injection. Its exhibition should be preceded by an enema of simple water, after a stool, so as thoroughly to wash out the rectum and allow access to every fold of the rectal mucous membrane. The official preparations are a tincture (TINCTURA QUASSIÆ—ten per cent., U. S.), dose, twenty drops to a teaspoonful (1.2–4 C.c.); an extract (EXTRACTUM QUASSIÆ, U. S.), dose, one to three grains (0.06–0.19 Gm.) ; and a fluid extract (EXTRACTUM QUASSIÆ FLUIDUM), dose, five to ten drops (0.3–0.6 C.c.).

GENTIANA—GENTIAN. U.S.

The root of Gentiana lutea, or the yellow gentian of the Alps. This root occurs in the shops either in pieces of various sizes and shapes, but generally several inches in length, or else in transverse slices. The texture is spongy, the odor faint but peculiar, and the taste bitter. It contains *gentisic acid*, which was discovered by Leconte and is tasteless and physiologically inert. The active principle is probably the *gentiopikrin* of Kromayer, a neutral, crystalline substance, of an intensely bitter taste.

THERAPEUTICS.—Gentian is one of the most efficient of the simple bitters, and may be used whenever such a remedy is indicated. It is never given in substance, but in one of its preparations. These are the compound tincture (TINCTURA GENTIANÆ COMPOSITA—ten per cent., U. S.), which contains gentian, bitter orange peel, and cardamom—dose, one fluidrachm to half a fluidounce (4–15 C.c.); the watery extract (EXTRACTUM GENTIANÆ, U. S.), dose, two to four grains (0.13–0.26 Gm.); and the fluid extract (EXTRACTUM GENTIANÆ FLUIDUM, U. S.), dose, ten minims to half a fluidrachm (0.6–2 C.c.). The compound infusion, formerly official, was a valuable preparation, containing some alcohol, and much used in doses of one to two fluidounces (30–60 C.c.).

CALUMBA—COLUMBO. U.S.

The root of Jateorhiza palmata, a climbing vine of Mozambique. It occurs in the shops in transverse disk-like slices, oval or circular in outline, one or two inches in diameter, of a spongy texture, having a yellowish surface, a very bitter taste, and a slightly aromatic odor. It contains a great deal of starch, besides berberine, and, it is said, in lesser amount, *columbin*, a bitter neutral principle crystallizing in rhomboid prisms or needles. F. Roux[5] has found that columbin given to pigeons in doses of ten centigrammes produces death, preceded by failure of the appetite, marked signs of gastro-intestinal irritation, and jaundice.

THERAPEUTICS.—A bitter, slightly aromatic tonic, useful as a stomachic in cases in which a simple bitter is indicated. It is not used in substance. Its preparations are—a tincture (TINCTURA CALUMBÆ—ten per cent., U. S.), dose, one to two fluidrachms (4–7 C.c.); and a fluid extract (EXTRACTUM CALUMBÆ FLUIDUM, U. S.), dose, fifteen minims to half a fluidrachm (1–2 C.c.).

CHIRATA, U. S., the herb and root of Swertia chirata, a plant growing in the northern part of India, is one of the best of the simple bitters, and is believed by some to exert a peculiar influence over the liver. Whenever a simple bitter is indicated, this drug may be employed, especially if a cholagogue action be desired. The solid extract is an excellent preparation in doses of one to two grains (0.06–0.12 Gm.); dose of the fluid extract (EXTRACTUM CHIRATÆ FLUIDUM, U. S.), five to ten minims (0.3–0.6 C.c.); of the tincture (TINCTURA CHIRATÆ—ten per cent., U. S.), a fluidrachm (4 C.c.).

PRUNUS VIRGINIANA—WILD CHERRY. U.S.

Wild cherry bark is the product of Prunus (Cerasus) serotina or wild cherry tree, not of Prunus Virginiana or choke-cherry, whose name it bears. It occurs in pieces of various sizes, usually without epidermis. The color is a reddish cinnamon; the taste slightly astringent, bitter, and peculiar, resembling that of peach-leaves. It contains tannic acid, bitter extractive, a nitrogenous, crystallizable, odorless glucoside (*Amygdalin*),

and an albuminous principle (*Emulsin*). When amygdalin in watery solution is brought in contact with emulsin, it is decomposed, forming prussic and formic acids and a colorless, thin, volatile oil, which, when pure, has a peculiar, agreeable odor and a burning taste. According to Liebig and Wöhler,[6] seventeen grains of amygdalin yield one of hydrocyanic acid: therefore, if thirty-four grains of amygdalin be mixed with sixty-six grains of an emulsion of sweet almonds, a two per cent. (by weight) solution of hydrocyanic acid will be formed.

PHYSIOLOGICAL ACTION.—Amygdalin is physiologically inert, as much as sixty grains having been taken without result. Fifteen grains may cause death in the rabbit, but this is owing to its being converted into prussic acid by the emulsin contained in the green herbage in the stomach of the rabbit.*

THERAPEUTICS.—In wild cherry bark properly administered there are three active ingredients,—tannic acid, bitter extractive, and prussic acid. The amount of prussic acid is too small to cause perceptible effects, so that wild cherry bark is simply a feeble astringent and tonic. It has been very largely used in *phthisis*, and has been supposed not only to act as a tonic and astringent, but also to exert a calmative influence on the nervous system.

The dose of the infusion (INFUSUM PRUNI VIRGINIANÆ—four per cent., U. S.) is one to two wineglassfuls (60–118 C.c.). The syrup (SYRUPUS PRUNI VIRGINIANÆ—fifteen per cent., U. S.) is practically inert, but is often employed as a vehicle. The dose of the fluid extract (EXTRACTUM PRUNI VIRGINIANÆ FLUIDUM, U. S.) is from half a fluidrachm to a drachm (2–4 C.c.).

AROMATICS.

The aromatic oils are essentially local irritants, causing when taken into the mouth intense burning pain, and when confined upon the skin, rubefaction, blistering, and finally, if the contact be very prolonged, more destructive changes. Internally, taken in very large doses, they cause burning pain in the stomach, increased activity of the circulation, and a species of intoxication. In sufficiently large quantities they are irritant narcotic poisons. When administered in therapeutic doses they act almost exclusively upon the alimentary canal. As compared with that of the simple bitters, their influence is more powerful and more transient. They do not permanently increase the digestive power, but simply increase action for the time being. They are employed chiefly to increase the immediate stimulant effect of bitter tonics upon the secretory digestive glands; as *carminatives*, to stimulate the intestines to contract upon and expel flatus; to prevent the griping of purgatives; to disguise the taste of medicines, and to render nauseating drugs acceptable to the stomach; and to act as condiments and aid in the digestion of the food.

* See Husemann (*Die Pflanzenstoffe*).

It is probable that aromatics directly after their ingestion affect more powerfully the digestive glandular apparatus than do bitter tonics, since Gottlieb[7] has shown that such substances as mustard, which are local irritants to the stomach, cause a very marked increase in the secretion of the pancreatic fluids. Even when the gland had almost ceased its function, oil of mustard introduced into the stomach or duodenum caused active secretion in the pancreas. Quassia, taken as a type of the bitters, had no effect on the pancreatic activity.

Injected into the circulation, most volatile oils lower the blood-pressure by depressing the heart's action, and even in comparatively small doses may cause immediate diastolic arrest. In this respect oil of cloves is one of the most powerful. Their cardiac action is undoubtedly direct and upon the heart itself: other muscular structures would seem to be similarly affected, as H. Kobert[8] has found that the oil of mace directly lowers muscular excitability.

When in concentrated form almost all of the volatile oils are direct paralyzants to nerve-tissues, and seem to act especially upon the sensory and peripheral nerve-endings; hence most of them are local anæsthetics, and some are used for this purpose in practical medicine. Most of them also possess antiseptic properties.

Some of the tonic drugs containing a volatile oil also have in them a bitter principle which modifies their action. Such drugs may be known as *aromatic bitters;* as bitters they are less powerful than such drugs as quassia, and are especially indicated when the stomach is delicate and easily nauseated.

Inflammation of the stomach or bowels is the chief contra-indication to the use of aromatics. Unlike the simple bitters, they are often very useful in *diarrhœa* of nervous irritability or of relaxation, when no decided inflammation exists.

CINNAMOMUM.—The U. S. Pharmacopœia recognizes as the barks of undetermined species of the genus Cinnamon, CINNAMOMUM CASSIA, *Cassia Bark*, *Chinese Cinnamon*, and the CINNAMOMUM SAIGONICUM, or *Saigon Cinnamon*, which comes from Cochin China; it also recognizes CINNAMOMUM ZEYLANICUM, or *Ceylon Cinnamon*, the bark of the Cinnamomum zeylanicum. Of these barks the Ceylon is considered the finest and the Cassia the poorest in quality. They all contain tannic acid and a yellowish volatile oil (OLEUM CINNAMOMI, U. S.), which on account of its great fragrance and very pleasant taste is largely used, in doses of from one to three drops (0.06–0.18 C.c.) as an adjuvant, or to disguise the flavor of less agreeable drugs. Cinnamon water (AQUA CINNAMOMI—oil 0.2 per cent., U. S.) is used solely as a vehicle. The spirit of cinnamon (SPIRITUS CINNAMOMI—oil ten per cent., U. S.) is administered in doses of one-half to one fluidrachm (2–4 C.c.); the tincture (TINCTURA CINNAMOMI—Ceylon Cinnamon—ten per cent., U. S.) in doses of one to two fluidrachms (4–7 C.c.). PULVIS AROMATICUS, U. S.—*Aro-*

matic Powder (cinnamon, ginger, cardamom, nutmegs) is an elegant carminative in doses of from ten to twenty grains (0.6–1.3 Gm.).

CARYOPHYLLUS. U. S.—*Cloves* are the unexpanded flowers of Eugenia aromatica, a tree growing in the Molucca Islands. OLEUM CARYOPHYLLI, U. S., is an exceedingly pungent, yellowish, volatile oil, becoming dark by age, which, besides being used as a carminative and an aromatic, is often employed to benumb sensitive dentine, or even exposed pulp, in *caries* of the teeth. Dropped on a piece of cotton and placed in the cavity, it will frequently cure *toothache*. Dose, one to two drops (0.06–0.12 C.c.). The infusion, or clove tea (two drachms to a pint), is made with boiling water ; dose, a wineglassful (60 C.c.).

MYRISTICA. U. S.—*Nutmeg* is the kernel of the fruit of Myristica fragrans, a tree growing in the Molucca Islands. The nutmeg contains both a fixed and a volatile oil. Mace (MACIS, U. S.) is the *arillus* or outer imperfect supernumerary coating of the seed. Both mace and nutmeg depend for their activity upon the volatile oil (OLEUM MYRISTICÆ, U. S.), which, when injected intravenously into the lower animals, causes loss of coördination, tremors, profound coma, abolition of all reflexes, and finally death from respiratory paralysis, its influence upon the circulation being comparatively feeble.* In man, one or two nutmegs will usually suffice to produce a dreamy, half-unconscious intoxication, and severe or even fatal poisoning has been caused by larger quantities. The symptoms of poisoning have been dizziness, stupor deepening into coma, muscular relaxation, dilated pupils, slow pulse and respiration, and suppression of urine, ending in death from respiratory paralysis.† Dose, of oil, ten to twenty drops (0.6–1.2 C.c.).

PIMENTA. U. S.—*Pimenta*, or *Allspice*, is the unripe berries of Pimenta officinalis, a tree, native of the West Indies. Dose of the volatile oil (OLEUM PIMENTÆ, U. S.), two to five drops (0.12–0.3 C.c.).

CARDAMOMUM. U. S.—*Cardamoms* are the fruit of Elettaria repens, which grows in the East Indies. They consist of tough, seemingly fibrous, generally more or less triangular dry and tasteless capsules, containing a number of small, hard, very aromatic seeds. The colorless, highly aromatic, volatile oil is not official. Cardamom is a very grateful aromatic, much less stimulating and heating than most of the other drugs of its class. The dose of the tincture (TINCTURA CARDAMOMI—ten per cent., U. S.) is one fluidrachm (4 C.c.). The compound tincture (TINCTURA CARDAMOMI COMPOSITA—two per cent., U. S.) is a very elegant

* Experiments of H. C. Wood ; also Cadeac and Meunier (*Journ. Méd. Vét.*, Lyon, 1890).

† Fatal case, *N. Y. Med. Record*, Nov. 1886.

addition to, or vehicle for, tonic medicines; dose, one to two fluidrachms (4–7 C.c.).

ZINGIBER. U. S.—*Ginger* is the dried rhizome or root-stock of Zingiber officinale, growing in the East and West Indies. *Green Ginger* is the *fresh* rhizome. *Black Ginger* is the root-stock dried with the epidermis on; *White* or *Jamaica Ginger* is the same, deprived of its epidermis. The fresher ginger is the greater is its power, and by time and exposure it becomes completely inert. Its active principles are a soft, acrid, aromatic resin, and a yellow, volatile oil. Ginger is much used in domestic medicine as a stimulant carminative in *colic;* given in hot water, it is also used as a sudorific and stimulant in the pain due to *suddenly suppressed menstruation.* It is often added with advantage to other remedies in *dyspepsia.* The syrup (SYRUPUS ZINGIBERIS—three per cent., U. S.) is used only as a cordial drink or vehicle, in doses of from half a fluidounce to a fluidounce (15–30 C.c.). The tincture, often called *Essence of Ginger* (TINCTURA ZINGIBERIS—twenty per cent., U. S.), is the most commonly employed preparation; the dose is half a teaspoonful to a teaspoonful (2–4 C.c.). The dose of the fluid extract (EXTRACTUM ZINGIBERIS FLUIDUM, U. S.) is five to ten drops (0.3–0.6 C.c.). The oleoresin (OLEORESINA ZINGIBERIS, U. S.) is used as a stimulant addition to tonic pills; the dose is from half a minim to two minims (0.03–0.12 C.c.).

PIPER. U. S.—*Black Pepper* is the unripe fruit of Piper nigrum, a woody vine-like plant growing in the East Indies. *White Pepper* is the ripe berries stripped of their skin and dried. It is much less pungent than the black pepper. The active principles of black pepper are a soft, acrid resin, a pungent, fiery, volatile oil, and piperin.

In 1819 Oersted discovered *Piperin* (PIPERINUM, U. S.), which crystallizes in colorless, glistening, four-sided, truncated prisms, of a neutral reaction, but capable of combining with acids to form salts. When pure it is tasteless; but very commonly it has a burning taste, due to the presence of some of the volatile oil of pepper. The possession of very active antiperiodic properties has been asserted for piperin, and it was for a time employed in *intermittent fever;* but it has fallen into complete disuse. The dose as an antiperiodic is four grains (0.26 Gm.), repeated once or twice during the interval between the paroxysms. Pepper is very largely used as a condiment; but, as its taste is more hot than aromatic, it is rarely given internally in medicine except as an addition to simple bitters or to antiperiodics, generally in the form of the oleoresin (OLEORESINA PIPERIS, U. S.), the dose of which is one-half to one grain (0.03–0.06 Gm.). In atonic *dyspepsia* the latter preparation is an excellent adjuvant to tonic pills. Schiffer is said (Fliess) to have used piperin successfully in a case of *vaginismus*, by injecting three-tenths of a grain (0.018 Gm.) hypodermically near the vaginal entrance. In

using piperin by hypodermic injections it is of the utmost importance to see that it is free from the oil of pepper.

CAPSICUM. U. S.—The U. S. Pharmacopœia now recognizes only the small,—less than an inch long,—very fiery fruit of Capsicum fastigiatum, the *African Pepper*, or *Chillies*. The large, bright red, conical or ovate, comparatively mild peppers of the market are from C. annuum ; they are sometimes known as *West India peppers*. Capsicum contains as its active principle an exceedingly acrid oleoresin.*

Capsicum is a very powerful local irritant, its oleoresin when applied to the skin producing in a very few minutes intense pain and redness, and finally destroying the cuticle. In the alimentary canal it acts in a similar manner : thus, moderate doses produce merely a pleasant feeling of warmth in the stomach, while overdoses may cause gastro-intestinal inflammation, with severe pain, as well as vomiting and purging, followed after a time by strangury and other evidences of genito-urinary irritation. The chief use of *Cayenne Pepper* is as a condiment ; yet it is often added with advantage to tonic pills to increase their immediate action on the stomach. When there is habitual feeble digestion, with flatulence, its free use on food may do good. In *adynamic diseases*, especially as occurring among *drunkards*, capsicum is often very useful by stimulating the stomach up to the point of digesting food. *Locally*, either as the diluted tincture in a gargle or applied in powder or tincture by means of a swab, it is useful in *severe tonsillitis*, especially in that accompanying scarlet fever. The dose of capsicum is four to five grains (0.26–0.3 Gm.) in pill ; of the very efficient oleoresin (OLEORESINA CAPSICI, U. S.), from one-quarter to one-half a minim (0.016–0.032 C.c.) ; of the tincture (TINCTURA CAPSICI—five per cent., U. S.), one-half to one fluidrachm (2–4 C.c.) doses to drunkards ; of the fluid extract (EXTRACTUM CAPSICI FLUIDUM, U. S.), one-half to one minim (0.03–0.06 C.c.).

OLEUM CAJUPUTI. U. S.—The *Oil of Cajuput* is obtained from the leaves of Melaleuca leucadendron, a tree growing in the Molucca Islands. This volatile oil is of a green color, a peculiar fragrant odor, and a burning, camphoraceous taste. It is not very irritating to the skin, but is exceedingly destructive to low forms of life, and consequently has been used as a *parasiticide* externally, and even internally against the Ascarides. In *intestinal pain* and *spasm* and in *serous diarrhœa* it is efficient, especially in combination with chloroform, camphor, and opium. As a counter-irritant, it has been used in *rheumatism ;* as a stimulant to the skin, in *psoriasis*, *acne rosacea*, and *pityriasis*. Dose, from ten to fifteen drops (0.6–1 C.c.).

OLEUM SASSAFRAS. U. S.—The *Oil of Sassafras* is largely used in the arts on account of its cheapness and pleasant flavor. It is capable of

* The name of *Capsicin* has been applied by different observers to the oil, to the resin, and to their combination, but has no definite meaning.

producing very marked narcotic poisoning,[9] and is said to act upon the lower animals as a convulsant and narcotic. John Bartlett [10] asserts that it is capable of inducing uterine contractions, and reports cases of abortion caused by it.

AURANTII AMARI CORTEX—*Bitter Orange Peel.* U. S.—The fluid extract (EXTRACTUM AURANTII AMARI FLUIDUM, U. S.) and the tincture (TINCTURA AURANTII AMARI—twenty per cent., U. S.) may be given respectively in doses of twenty minims (1.2 C.c.) and a fluidrachm (4 C.c.). AURANTII DULCIS CORTEX—*Sweet Orange Peel.* U. S.—Of the syrup (SYRUPUS AURANTII—five per cent., U. S.) the dose is a dessertspoonful (7 C.c.), of the tincture (TINCTURA AURANTII DULCIS—twenty per cent., U. S.) a tablespoonful (15 C.c.). The orange peels are themselves scarcely medicinal, but are official as affording preparations much used as vehicles. LIMONIS CORTEX, U. S., or *Lemon Peel* (SPIRITUS LIMONIS—five per cent., U. S.), is also used for flavoring purposes.

AURANTII FLORES.—The flowers of the orange are official for the preparation of *Orange Flower Water* (AQUA AURANTII FLORUM, U. S.), which is used as an elegant vehicle, free from medicinal properties.

The fruits of the following umbelliferous plants—Fœniculum capillaceum, Carum carui, Coriandrum sativum, and Pimpinella anisum—are official under the respective names of FŒNICULUM (*Fennel*), CARUM (*Caraway*), CORIANDRUM (*Coriander*), and ANISUM (*Anise*). They all depend for their virtues upon volatile oils which are official. The oil of anise of commerce is largely the product of a Chinese tree, the Illicium anisatum, or Star Anise, from whose five- to ten-rayed capsular fruit it is obtained by distillation. The AQUA FŒNICULI (0.2 per cent.) and the SPIRITUS ANISI (ten per cent.) are official. All of these fruits and their preparations may be used as carminatives and stomachics.

The herbal portions of the following mints are official: Salvia officinalis, Mentha piperita, Mentha viridis, and Melissa officinalis. They are respectively known as *Sage* (SALVIA), *Peppermint* (MENTHA PIPERITA), *Spearmint* (MENTHA VIRIDIS), and *Balm* (MELISSA). The important U. S. preparations of them are as follows: AQUA MENTHÆ PIPERITÆ (*Peppermint Water*) and AQUA MENTHÆ VIRIDIS (*Spearmint Water*), both very frequently used as vehicles. SPIRITUS MENTHÆ VIRIDIS and SPIRITUS MENTHÆ PIPERITÆ (*Essence of Spearmint* and *Essence of Peppermint*), used as carminatives, in doses of from ten to twenty drops (0.6–1.2 C.c.). The *oils* of lavender,* peppermint, and spearmint are

* Masoin and Bruylant have studied to some extent the physiological action of the *oils of lavender, rosemary, marjoram,* and *aspic* (*Lavandula spica* L.) (*Bull. Acad. Roy. Méd. de Bruxelles,* 1879, 558; see also *Schmidt's Jahrb.*, clxxx. 123, and Cadeac

also official, and may be used in doses of from three to ten drops as carminatives. The oil of peppermint has been long used in China as a local application in *neuralgia* and *subacute rheumatism*, and is sometimes very effective in relieving pain. It should be applied to the part until the burning is no longer endurable, when it may be removed and petrolatum applied. (See also MENTHOL.) SPIRITUS LAVANDULÆ (*Spirit of Lavender*), a very elegant and agreeable stomachic and cordial, is made by dissolving oil of lavender flowers in alcohol. Dose, a fluidrachm to half a fluidounce (4–30 C.c.). Sage contains tannin.

Water of Rosemary has long been believed to have especial influence upon the skin, and in cases of *acne* a lotion composed of a pint of this water and an ounce of the flowers of sulphur has been often effective.

AROMATIC BITTERS.

ANTHEMIS. U.S.—CHAMOMILE.

Roman or *true Chamomile* is the dried flowers of Anthemis nobilis, a composite of Europe. They are sometimes single, sometimes double. The single are more aromatic than the double florets. Chamomile contains a bluish or sometimes greenish volatile oil, a bitter principle, and a small amount of tannin. The infusion (one ounce to a pint) is an excellent, mild stomachic in doses of one to two wineglassfuls. MATRICARIA, U. S., or *German Chamomile*, the flowers of Matricaria Chamomilla, resembles true chamomile in odor, taste, and therapeutic uses, but is less agreeable and effective.

SERPENTARIA. U. S.—*Virginia snakeroot* is the root of Aristolochia Serpentaria and of A. reticulata, small herbal plants of the United States. It occurs as fine brittle rootlets attached to a small head, of a camphoraceous odor and taste, and contains a volatile oil, a yellowish-green resin, and a bitter principle. It is an elegant stimulant tonic, especially useful as an adjuvant to more powerful bitters. In overdose it is said to cause vomiting and even purging. The dose of the tincture (TINCTURA SERPENTARIÆ—ten per cent., U. S.) is one to two fluidrachms (4–7 C.c.); of the fluid extract (EXTRACTUM SERPENTARIÆ FLUIDUM, U. S.), twenty drops (1.2 C.c.).

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and Meunier, *Compt.-Rend. Soc. Biolog.*, 1889, and *Lyon Méd.*, 1889). In frogs they caused generally paralysis, with loss of reflex activity, the muscles being intact, and the sensory nervous apparatus being affected before the motor. Upon the higher animals a similar effect was produced, except that oil of rosemary caused epileptiform convulsions. *Oil of Peppermint* (*M. piperita*) has been studied by S. D. Markuson (*Inaug. Dis.*, Halle, 1877; *Schmidt's Jahrb.*, clxxx. 122), who finds that while very small doses increase, larger ones decrease the blood-pressure and lower the bodily temperature. Most of the volatile oils have germicidal properties, and the oil of peppermint has been highly praised as a practical dressing for *burns*, *wounds*, etc. (See *The Medical Reporter of India*, vi.)

CASCARILLA, U. S., is the bark of Croton Eluteria, a shrub growing in the West Indies. It contains tannin, volatile oil, and *cascarillin*, a neutral, bitter, crystallizable principle, and acts similarly to serpentaria. The dose of the infusion (INFUSUM CASCARILLÆ—one ounce to a pint) is a wineglassful (60 C.c.).

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FAMILY II.—EMETICS.

EMETICS are those drugs which are employed in the practice of medicine for the purpose of producing emesis, or vomiting.

Vomiting occurs under two provocations, or in two manners. Thus, a mental impression, or a disordered state of the blood, may influence the nerve-centres directly, and emesis, spoken of as *centric*, results ; or a peripheral irritation in the stomach itself, or in some other organ, as in the kidneys, may induce vomiting precisely similar in the method of its production to the more ordinary reflex movements ; such vomiting is called *reflex* or *excentric*.

Emetics produce their results in both of these methods. Thus, tartar emetic has been believed to affect the centres directly, so as to cause centric vomiting, while copper sulphate has been believed to irritate the mucous membranes of the stomach, so as to produce reflex vomiting. Much doubt, however, has been thrown upon the old views, and it is probable that most emetics have a double influence. Thus, the purging of veratria or of tartar emetic is almost certainly connected with its elimination, and is probably due to a direct action of the circulating poison upon the intestinal mucous epithelium, gland-cells, and peripheral nerves. It seems *a priori* almost a necessity that the vomiting caused by these poisons is produced in the same way as is the purging. D'Ornellas has found that when emetine is injected into the veins of animals the vomiting occurs simultaneously with the elimination of the alkaloid from the gastric mucous membrane, and asserts that Kleimann and Simonowitsch have determined the same thing with antimony. Further, antimony seems to cause vomiting partly by acting upon the centres, partly by irritating the peripheral nerve. Irritant emetics are more prompt than those which chiefly affect the nerve-centres ; they always cause less nausea and general systemic disturbance than do the centric emetics.

Another evident practical fact is, that while centric emetics will act in whatever way they are introduced into the system, the mechanical emetics must be exhibited by the stomach. Thus, apomorphine may be given by hypodermic injection, but mustard must be taken by the mouth. Nevertheless, it is probable that most of the so-called "irritant emetics" act in part by being absorbed, since A Sacher[1] has found that even zinc sulphate will, when injected in proper dose into the blood, produce

vomiting, and Brunton and West have demonstrated that a peptone of copper injected into a vein causes violent vomiting.

A very curious property of emetics has been pointed out by E. Harnack,[2] who, as the result of an elaborate investigation, affirms as a law that all specific emetic substances destroy, even when in relatively small dose, the excitability of striated muscular fibre. Harnack seems to establish the general truth of this; but that it is a universal law is scarcely probable, and the connection between the two properties is very obscure. According to H. Kobert,[3] antimony has an effect on muscle-fibre only when the contact is prolonged.

In regard to the phenomena of vomiting, there are a few points to which it is necessary here to call attention. First of these is the fact that *nausea* always produces, or is accompanied by, muscular relaxation. Vomiting may take place, as from mustard, without much relaxation; but when it is accompanied by much nausea the whole system is, as it were, unbent, the skin relaxed and bedewed with perspiration, the pulse soft and feeble, the muscular system limp and incapable of exertion, and the mental acts almost suspended. During violent vomiting the blood is driven to the head, so that the whole exterior of the cranium, and probably the interior also, becomes very much congested. The abdominal circulation is greatly affected, and the blood is, as it were, squeezed out of the portal vein and its tributaries. The matters rejected consist of the contents of the stomach, and, in repeated vomiting, also those of the duodenum. The secretion from the gastric mucous membrane is very much enhanced, and without doubt is more or less modified. Bile in ejecta is to be recognized by the green color and the bitter taste, or more infallibly by testing with the proper reagents.

The indications for the use of emetics are as follows:

1. *To unload the Stomach.*—For this purpose they are employed in poisoning, or when the stomach is oppressed by indigestible substances or by its own acrid, perverted secretions. The symptoms induced by irritating materials in the stomach are various, and sometimes it requires a good deal of tact or experience to recognize their cause. Among them may be mentioned a feeling of weight or load in the stomach, gastric distress, or severe cramp or spasmodic pains, with or without some nausea and retching. In other cases no local manifestations of trouble may be present. Thus, *convulsions* in children are very frequently the result of gastric irritation, and are at once relieved by emptying the stomach. In adults, *apoplectiform coma* may offer a similar history. Occasionally *urticaria*, or hives, and not rarely severe *headache*, have a similar origin, and require a similar treatment.

2. *To affect the Abdominal Viscera and Circulation.*—In *congestions* of the *portal* circulation, especially such as follow a debauch, and in the condition of digestive derangement known as *biliousness*, emetics are often of service. In *catarrhal jaundice* they may effect much good by causing dislodgement of the mucus plugging the ducts. They have

been employed in cases of *biliary calculi;* but the chances of forcing out the calculus by external violence are probably no greater than those of lethal rupture of the gall-bladder.

3. *To dislodge Substances from the Respiratory Passages.*—For this purpose emetics are sometimes used when foreign bodies have found entrance into the larynx ; but it is chiefly in *membranous croup* that the present indication is met with. The emetics chosen for this purpose should be such as act with violence without producing much nausea or systemic disturbance : the mechanical emetics are therefore the best.

4. *To produce Muscular Relaxation.*—The introduction of anæsthesia has rendered the use of emetics to meet this application almost obsolete. Occasionally, however, in *asthmatic* or other *spasmodic affections* of the respiratory organs, emetics are still employed. For this purpose the drugs causing much nausea are preferred. In adults, lobelia is the best ; in children, ipecacuanha. Nauseating rather than emetic doses should be employed.

Contra-indications.—The chief contra-indications to the use of emetics are the existence of congestion of the brain and of gastric inflammation. Advanced pregnancy, and hernia, while they do not positively contra-indicate the use of emetics, should cause great caution to be practised in their employment.

Administration.—Emetics should, as a general rule, be given in a full dose, so as to avoid unnecessary repetition, and should be administered dissolved in water or in syrup. Their action should be assisted by frequent and copious draughts of tepid water, which also have the advantage of rendering the vomiting less painful. When for any reason protracted nausea is desired, the doses should be small and repeated at short intervals.

Hyperemesis may advantageously be divided into two varieties : first, such as is due to overdoses of depressing centric emetics ; second, such as arises from irritation of the stomach, as by mechanical emetics. The treatment of the first of these consists in the enforcement of absolute quiet in the horizontal position, the free use of opium enemata, the application of counter-irritants to the epigastrium, and the use of alcoholic stimulants. The latter should be given in hot water, and should not be too much diluted. We have seen raw brandy arrest at once the most alarming centric emesis after the failure of other methods. Cocaine, creosote, chloroform, or chloroform and volatile oils are sometimes of value in this form of hyperemesis. When excessive vomiting is due to some irritant substance, the stomach should be thoroughly washed out by large draughts of warm mucilage, opium given by the rectum, a mustard plaster or blister, or, often better still, leeches applied to the epigastrium, and no medicine at all be taken into the inflamed viscus. The swallowing of small pieces of ice is sometimes of service. If these remedies fail, the treatment of this form of hyperemesis soon resolves itself into that of gastritis.

CENTRIC EMETICS.

IPECACUANHA. U.S.

The root of Cephaëlis Ipecacuanha, a small, shrubby plant, growing in Brazil, where the drug is gathered by the Indians, to be exported in large bales or bags. Ipecacuanha occurs in pieces two or three lines in thickness, variously bent and contorted, marked on their surface with numerous prominent rings, and composed of an outer, thick, active, hard, and horny cortex, and an inner, light, inert, woody centre. Varieties of ipecacuanha—the *red*, the *gray*, and the *brown*—have been formed from the color of the bark, but the distinction is trivial. The root has very little odor, but the brown powder has a decided and peculiar smell, and in some persons excites sneezing, or even violent asthmatic dyspnœa. The taste is bitter, acrid, and nauseous. In 1817 Pelletier described an alkaloid in ipecacuanha which he called *emetine*. According to the later researches, however, this alkaloid is really composed of three alkaloids, the most important of which are *emetine* and *cephaëline*. The emetine of physiological investigators and of the text of this book is the mixed alkaloids,—*i.e.*, the emetine of Pelletier.

Local Action.—Absorption and Elimination.—Locally applied, ipecacuanha is a decided irritant, manifesting its action not only upon mucous membranes and upon denuded surfaces, but also causing, when applied by inunction, an eruption of small, discrete pustules, with a rather large areola, followed, it may be, by large pustulation and even severe ulceration. Ipecacuanha rapidly yields its active principles to absorption. They are probably eliminated by the stomach, intestines, and kidneys, but concerning this we have no definite knowledge.

Physiological Action.—When given in small repeated doses to man, ipecacuanha produces malaise, with nausea, and perhaps an increase of the secretions of the salivary glands and of the mucous membranes of the bronchial tubes and of the stomach. In large amounts it causes vomiting, accompanied by only a moderate amount of nausea, but by a decided increase of the secretions mentioned above. The vomiting, even when very large amounts are taken into the stomach, is not apt to be severe, nor the prostration marked,—no doubt because the excess of the drug is rejected before absorption.

The general physiological action of ipecacuanha is very feeble, and in its details not thoroughly understood.

According to D'Ornellas,[4] Merck's commercial emetine in toxic doses (0.03 milligramme) produces in frogs dryness of the skin, swelling of the abdomen, diminution of the circulation and respiration, increased rather than diminished sensibility, muscular feebleness deepening into abolition of voluntary movement, with at first increased and afterwards diminished reflex activity, and finally death from failure of respiration, the heart continuing to beat often for many hours. In mammals the symptoms induced by the poison in large doses are very similar to those just detailed, except that emesis is usually violent, but in some cases it is wanting.

Nervous System.—Respiration.—Circulation.—Upon the cerebrum ipecacuanha exercises no perceptible influence : D'Ornellas and Pecholier have found that in the frog both nerves and muscles retain their susceptibility to feeble galvanic currents, and they correctly reason that the paralysis which the poison produces is of spinal origin. D'Ornellas and Pecholier are in direct contradiction in regard to the action of the drug upon sensibility.

D'Ornellas, Pecholier, and Foulkrod[5] are in accord in asserting that the toxic dose of emetine kills by asphyxia ; so that it probably is, when in overwhelming amount, a centric respiratory paralyzant.

In the mammal the toxic dose of emetine frequently produces a fall of arterial pressure (Pecholier and Foulkrod). As shown by Dyce Duckworth, however, this does not occur until late in the poisoning ; it is certainly in part of cardiac origin, since a half-grain of emetine injected into the jugular vein of the dog will cause an immediate death from cardiac paralysis, and since it occurs after previous section of the spinal cord (Foulkrod). Nevertheless, the influence upon the heart-muscle must be very feeble, since the frog's heart often retains after fatal poisoning its irritability for many hours after death (D'Ornellas). It is probable, though not proved, that the muscle-fibre in the vessel-walls shares the cardiac action of the poison. The assertion which has been made, that the small dose of emetine causes vaso-motor spasm, rests upon insufficient evidence, and is in all probability incorrect, the therapeutic dose having no decided influence upon the arterial pressure.

Pulmonic and Digestive Organs.—As emetine injected hypodermically causes vomiting, ipecacuanha must be looked upon as a centric emetic ; but the observation of D'Ornellas, that the emetine produces vomiting much more slowly when thrown into the veins than when given by the stomach, indicates that the local irritant action of the drug is a factor in the production of emesis.

The great influence of the drug upon the abdominal viscera is further shown by the fact, attested by Pecholier, Dyce Duckworth, and D'Ornellas, that in emetine-poisoning, although there is a distinct fall of temperature in the mouth and on the surface of the body, in the intestines the temperature either remains stationary or, more commonly, rises. Again, the changes found after death from emetine are almost exclusively in the lungs and digestive organs.

Pecholier, in his earlier experiments, found great paleness of the lungs, with intense hyperæmia of the stomach and the upper half of the intestines, but in some of his later experiments the lungs were profoundly influenced. Dyce Duckworth especially noted intense hyperæmia of the lungs, which were in some places emphysematous, but in other portions collapsed and even affected with true consolidation. The lesions were much less marked in the intestines than in the lungs, which resembled very closely those taken from the bodies of animals killed by section of the vagi. The pulmonic lesions were found to be most intense in the rabbit ; the intestinal, in the dog, cat, and guinea-pig. Magendie forty years ago recorded

the pulmonic lesions of emetine-poisoning, and D'Ornellas has likewise recorded them, but has also seen cases in which ischæmia of the pulmonary tissue was found after death.

It is evident that the poison has an especial action upon both lungs and intestines; but why the pulmonic lesions should so vary is not at present known. The occurrence of these changes in the pulmonary tissues is in accord with clinical experience, which teaches most decidedly that ipecacuanha has an action upon the pulmonary and gastro-intestinal mucous membranes.

THERAPEUTICS.—Whenever it is desired to unload the stomach or to act by emesis upon disease, without inducing much prostration, ipecacuanha is the best of the emetics. In *narcotic poisoning* it is less certain than the "mineral emetics," but, as it produces no irritation of the stomach, it can be given more freely than they can, and is constantly used as an adjuvant to them. It is especially useful in the diseases of children, never causing the serious depression which tartar emetic is so apt to produce. When, however, very violent emesis is desired, as in *membranous croup*, other emetics, such as zinc sulphate, are to be preferred on account of the greater force of their action.

In *sick stomach* of nervous origin, such as occurs in *pregnancy*, minute doses of ipecacuanha have so often met with success that there can be no doubt of their value. One drop of the wine in a teaspoonful of water should be given every fifteen minutes. The use of ipecacuanha as an expectorant will be spoken of under that heading.

One of the most important uses of ipecacuanha is in *acute dysentery*, all forms of which have been treated with it with asserted advantage. Its beneficial action is most obvious in *bilious dysentery* and in *malignant dysentery*, as is indicated by the fact that its use is most common in tropical climates. In *sthenic inflammatory dysentery* it seems to be less available, although even in this it has been strongly advocated. In a valuable clinical paper, A. A. Woodhull[6] brings forward strong evidence of the value of the remedy not only in dysentery, but also in *choleriform diarrhœas*. It has likewise been used with great success in *hepatic torpor* and other forms of abdominal glandular derangement.

It probably influences not only the intestinal glands, but also the liver, since Pecholier[7] affirms that in animals killed by it no hepatic glucose can be found. Moreover, great advantage from its use may often be obtained in the condition known as *biliousness*. In *bilious dysentery* it will often produce large tarry discharges; a change in the color of the stools sometimes follows its use in *catarrhal jaundice*. The mechanical effect of the vomiting induced by it in these cases, however, must not be lost sight of; yet it does not seem to us sufficient to account for the results, especially as some observers state that the effects noted are produced even when little or no vomiting occurs. It has been proved by D'Ornellas and Pecholier that when emetine is introduced into the circulation or into the cellular tissue it escapes with the secretions of the stomach and bowels; so that the changes which are provoked in these organs are evidently connected with the elimination of the drug.

In 1890 Surgeon-Major Harris[8] used in dysentery the ipecacuanha root, deprived of its emetine, with alleged excellent results. His paper has given rise to considerable discussion, and Surgeon-Captain Walsh,[9] as the result of his experiments, came to the contrary conclusion that the value of ipecacuanha in dysentery depends upon its emetine, and devised a method of giving emetine in combination with biniodide of mercury, affirming that in this combination the drug does not produce vomiting. Other clinicians, however, have confirmed the statements of Surgeon-Major Harris. When the ipecacuanha root has been de-emetinized it fails to produce vomiting, or causes only very slight vomiting; and according to the clinical studies of Kanthack and Caddy,[10] it has all the curative effects of ipecacuanha in *dysentery*, and does not cause depression. The freedom from alkaloid of this so-called de-emetinized ipecacuanha seems to us very doubtful.*

As a *hæmostatic*, ipecacuanha has been recommended by Trousseau, and Pecholier[11] asserts that in *hæmoptysis* it is a specific.† It has been given with asserted advantage in *flooding* after child-birth, and Carrigen[12] asserts that it possesses oxytocic powers.

ADMINISTRATION.—As an emetic, ipecacuanha is generally administered in powder, thirty grains (2 Gm.) being given every fifteen or twenty minutes until the desired effect is produced. For a child a year old the emetic dose is five grains (0.3 Gm.). Its action should be aided and hastened by large draughts of lukewarm water. As a nauseant the dose is from two to five grains (0.13–0.3 Gm.). In dysentery it is generally best to begin with a full emetic dose, or with ten grains repeated every half-hour until emesis is produced. Two or three hours after vomiting, fifteen drops of laudanum should be exhibited, followed in twenty minutes by five to ten grains of ipecacuanha in *pill form;* this should be repeated every two or three hours, the amount of the opium being lessened, and that of the ipecacuanha increased, according to circumstances. The object is to have as much of the ipecacuanha retained as possible. Another plan is to give larger doses (twenty grains), repeated every two, four, or six hours, mustard being applied to the epigastrium and opium exhibited as before; and it is said that after two or three doses tolerance is established and the drug retained. In India, enemata of ipecacuanha are often employed, either as a substitute for or an adjuvant to its use by the mouth. This treatment has recently been imitated by Chouppe[13] and others, and in our own practice found to be satisfactory. It undoubtedly often succeeds in *dysentery* and *choleriform* and *chronic diarrhœas*, and the gastric symptoms are almost always avoided. In chronic cases the repetition of the enemata sometimes produces so much local irritation as to forbid their continuance. We have been accustomed to give a scruple of the powder with starch and laudanum, repeated every four hours. A decoction of the drug is to be preferred, as probably causing less local irritation and being more thoroughly absorbed. To an adult, Chouppe gives daily two injections of a decoction, each lavement representing two and a half drachms of the drug.

* See especially A. A. Woodhull (*Atlanta Med. and Surg. Journ.*, 1875).
† Consult *Pacific Med. and Surg. Journ.*, 1876.

As a counter-irritant, ipecacuanha is rarely used in this country ; but in England a liniment is employed composed of four parts of the powder to fourteen parts of olive oil.

The preparations for internal use are : a syrup (SYRUPUS IPECACUANHÆ—seven per cent., U. S.),—dose, as an expectorant, five to twenty minims (0.3–1.3 C.c.) ; a wine (VINUM IPECACUANHÆ—ten per cent., U. S.),—emetic dose, four fluidrachms to a fluidounce (15–30 C.c.); and a fluid extract (EXTRACTUM IPECACUANHÆ FLUIDUM, U. S.),—dose, as an emetic for an adult, thirty drops (2 C.c.). TROCHISCI IPECACUANHÆ, U. S., and TROCHISCI MORPHINÆ ET IPECACUANHÆ, U. S., are used in catarrh of the throat as a local application.

Emetine has been used in doses of from one-twelfth to one-sixth of a grain (0.005–0.01 Gm.), but it is very harsh and without advantage in its action.

APOMORPHINÆ HYDROCHLORAS—APOMORPHINE HYDROCHLORATE. U.S.

Apomorphine, discovered by Matthieson and Wright,[14] occurs as a snow-white powder, which is permanent when dry, but when moist or in solution soon becomes green, and finally almost black.

General Effects.—In man, apomorphine acts as a prompt emetic, the vomiting being accompanied by no symptoms of such nature as to be at all characteristic of the drug, unless it be excessive secretion from the salivary, nasal, and lachrymal glands. Very rarely great cardiac depression has been produced, but there is reason to suspect that this has been due to decomposition products.

PHYSIOLOGICAL ACTION.—*Local Action.*—The soluble salts of apomorphine, when pure, are not irritant, and when used hypodermically should not cause pain. They are absorbed with great rapidity. Concerning their elimination we have no definite knowledge.

In frogs, one to five milligrammes of apomorphine cause restlessness, followed by an increasing sluggishness and muscular weakness that may end in real or apparent death. In some instances there are violent convulsions, both clonic and tonic in character.* Sometimes recovery occurs after both respiration and cardiac action have apparently ceased.

In dogs, one to two milligrammes cause vomiting, without any other decided symptoms ; after slightly larger amounts, the vomiting is severe, and accompanied by free salivation and muscular tremblings. After very large doses, vomiting does not occur, but a condition of intense restlessness, the animal jumping, running, howling, and champing constantly. The slightest noise or alarm throws the animal into violent excitement and terror ; with pupils dilated and ears drawn stiffly back, he endeavors to get out of the apartment, and even to climb the wall. After still larger amounts (four or five grains), to this excitement is soon added failing muscular strength, and the hind legs are dragged behind the animal in his movements. The respiration is exceedingly hurried, and convulsions are suddenly developed. The paresis and convulsions increase, so that the animal lies upon his back, kicking

* G. Valentin (*Arch. f. Exper. Path. u. Pharm.*, xi. 399).

wildly into the air, and finally dies asphyxiated. Rabbits cannot vomit, but the general symptoms produced by the alkaloid in them and in cats are exactly parallel with those just described as occurring in the dog. Very small doses (ten milligrammes, Harnack) suffice to kill the rabbit. On chickens and pigeons, according to C. David,[15] it acts very much as it does upon dogs; the stage of excitement is very marked. After death no distinct lesions are to be found, unless, as Quehl[16] believes, there is habitually an excessive hyperæmia of the pons Varolii.

To the therapeutist the chief interest in apomorphine is in connection with its power of producing vomiting; but before taking this up we shall briefly review what is known in regard to its general actions.

Nervous and Muscular Systems.—The action of apomorphine upon the cerebrum seems to be that of a primary stimulant delirifacient and final paralyzant. The cause of the convulsions at present cannot be considered as determined.* According to Reichert's experiments, both the sensory and motor nerves are first stimulated and afterwards paralyzed. In opposition to the experiments of Quehl, Harnack[17] found that apomorphine directly affects the voluntary muscles, and as his experiments have been confirmed by Reichert, there can be no doubt that apomorphine is a muscle-poison.

Circulation.—The reports upon the action of this drug on the circulation are somewhat discordant. It appears to be proved that the therapeutic dose does not affect the blood-pressure, but, contrary to the statements of Seibert,[18] Max Quehl, and Bourgeois,[19] it has been shown by Harnack and by Reichert[20] that the toxic dose does lower the arterial pressure and is a direct paralyzant of the cut-out frog's heart. Reichert has shown that the mammalian heart is similarly affected by the drug, and the final fall of pressure must be at least in part of cardiac origin. Reichert states that preceding the fall of pressure there is a distinct rise, which is prevented by previous section of the cord, and is, therefore, probably due to stimulation of the vaso-motor centres. The pulse-rate is markedly increased by small and large doses of apomorphine, the maximum usually being reached about the time vomiting is fairly established; subsequently, in poisoning, the pulse falls below normal. Reichert believes the rise to be due to stimulation of the accelerators, and the fall to the influence upon the heart-muscle.

Respiration.—Usually the respiration-rate is increased by decided or toxic doses. During the convulsive period of the poisoning the respirations become irregular and unequal, and they finally grow more and more shallow and infrequent, until death results from a paralysis of the respiratory centres. Both Harnack and Reichert have noted that in the rabbit previous section of the par vagum does not prevent, but rather increases, the respiratory acceleration; Reichert affirms that in the cat

* The only one who has carefully studied them is Reichert, and his published account is self-contradictory. He reasons that the convulsions are chiefly spinal, and yet says that in mammals, after section of the spinal cord, except "in very exceptional cases," they are confined to the anterior part of the body.

and dog no increase of the respiration-rate occurs under the action of the drug if the pneumogastrics have been cut.

Temperature.—The action of apomorphine upon the temperature appears to be very trifling and inconstant. According to Ziolkowski,[21] the bodily heat usually falls after large doses from 0.1° to 0.5° C. Moerz noticed in one man that the temperature rose during the vomiting 0.2°; while Bourgeois affirms that in man the drug has no influence over the temperature, and Reichert has seen in animals a rise follow the hypodermic but not the intravenous injection of the alkaloid.

Emesis.—Gee[22] was the first to announce that apomorphine is a certain and prompt emetic, producing but little nausea, and having the great advantage of acting in very small dose, a tenth of a grain being sufficient, when injected under the skin, to cause vomiting in ten minutes. The time required for action depends largely upon the amount of the drug exhibited. After very small doses twenty minutes may elapse; and in Bourgeois's experiments 0.45 grain produced violent vomiting in less than two minutes. After these large doses the emesis usually recurs once or twice at intervals of a quarter to half an hour.* The vomiting seems to be of centric origin, as Reichert has succeeded in producing it when the thoracic aorta was tied so as to prevent any of the poison from reaching the stomach.

THERAPEUTICS.—Apomorphine is a safe and reliable emetic, and may be used whenever it is desired simply to empty the stomach. Apomorphine has a tendency in bronchitis to cause free secretion, and is especially useful in the *suffocative catarrh* of infants, when an emetic is required to get rid of the bronchial exudation. Under these circumstances it is said not only to act efficiently as an emetic, but also to render the mucus more copious and fluid.

Probably because it has morphine in its name there was at one time a rather wide-spread belief that apomorphine was not a suitable emetic in narcotic poisoning. In fact, however, narcotics influence the action of apomorphine only as they do that of every other emetic. Apomorphine may, therefore, be used in any poisoning: hypodermically given, it is often especially useful as a reinforcement of a mechanical emetic exhibited by the mouth.

ADMINISTRATION.—As an emetic, apomorphine has usually been administered hypodermically, in doses of one-tenth of a grain (0.006 Gm.), repeated every ten minutes until some effect is induced; but it may be exhibited by the stomach in double the amount. In cases of severe poisoning, where time is of great moment, it may be well to give as much as one-fourth of a grain (0.016 Gm.) at a single injection. In feeble persons, however, caution must always be exercised in using it, as one-fifteenth of a grain has caused death in seven minutes in an adult, fifty-four years old, suffering from chronic bronchitis with marked em-

* For the doses required to vomit various animals, see *Gaz. Méd.*, 1874, 466.

physema.[23] The expectorant dose is one-sixteenth of a grain (0.004 Gm.). Care must be exercised in its use in children. Loeb[24] gave hypodermically 0.03 grain to an infant, thirteen months old, suffering from capillary bronchitis: the free vomiting which was induced left the infant much exhausted. In a very few cases apomorphine has failed to vomit, and even caused startling symptoms: so that care should be exercised not to push the remedy too far. Carville affirms that three-tenths of a grain has caused a syncopal condition in an adult, and Prevost[25] details a case in which syncope and threatening collapse were apparently induced by a very small dose. In children especially must care be exercised, since, according to Harnack, the drug is very liable to produce collapse. Greenish preparations of apomorphine should not be used unless the dose be very small. Constantine Paul states that if glycerin be used as the sole menstruum the solution will keep three or four days. Carville[26] affirms that glucose acts well as a preservative, and it is also asserted that a few drops of muriatic acid will suffice.

MECHANICAL OR STIMULATING EMETICS.—The only drugs of practical value in this group are mustard flour and zinc sulphate; copper sulphate being so irritant as to be dangerous, and alum and other drugs sometimes used too uncertain in their influence.

Mustard flour is very prompt and even violent in its action, and is to be used when it is desired simply to evacuate the stomach rapidly. As it is generally to be had at once, it is especially useful in such emergencies as *narcotic poisoning*. Dose, a heaped tablespoonful in half a pint of water, repeated, if necessary, in ten minutes.

Zinc sulphate is a very sure emetic, much used in narcotic poisoning, especially with ipecacuanha or apomorphine. Dose, thirty grains (2 Gm.) dissolved in about two ounces of water: it may be repeated in fifteen minutes, if necessary.

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FAMILY III.—CATHARTICS.

PURGATIVES, or cathartics, are those drugs which are employed in medicine to produce purgation, or catharsis. The question whether they act by increasing the intestinal secretions or the peristaltic movements has been much discussed.

Thiry[1] experimented upon the subject of catharsis by drawing out a knuckle of intestine through a wound in the linea alba, cutting it free from the remainder of the gut without injuring its nerves or blood-vessels, sewing together the distal and proximal ends of the main portions of the intestines so as to reform a continuous tube, and then, after closing up one end of the knuckle, forcing the other into the wound so as to make an intestinal *cul-de-sac* which could be studied through a fistulous opening. In dogs which had recovered after this operation, Thiry found that large doses of magnesium sulphate, of senna, or of croton oil failed alike to increase the secretion of the separated piece of intestine, although they induced violent purging; further, that neither concentrated solutions of Epsom salt nor infusion of senna, even though kept in the *cul-de-sac* for some time, were able to increase its secretion by exosmose. More recently, S. Radziejewski[2] has made an elaborate investigation of the subject. As the result of a number of very careful analyses, he asserts that there is nothing to be found in the stools produced by magnesium sulphate, calomel, castor oil, croton oil, senna, or gamboge to indicate that they are anything besides the ordinary contents of the upper and lower bowels. Radziejewski confirms the fact observed by C. Schmidt, that the stools of purgatives contain a great deal of soda, but denies that this proves that they are transudations, asserting that the alkaline salts are derived simply from the pancreatic fluid. Radziejewski also corroborates the confirmation by Asp[3] of the discovery of Moreau,* that division of the intestinal nerves is followed by free serous exudation into the gut, but denies that purgatives act by paralyzing the vaso-motor nerves, because croton oil injected into a loop of intestine which had been separated by two ligatures from the remainder of the gut caused both vomiting and purging. As no emulsifying substance was contained in the intestine, he declares that no absorption could have occurred, and that consequently the general intestinal disturbance was simply due to increased peristaltic action, caused by the internal local irritation of the oil propagated along the intestines. The experiments of Thiry have also been repeated by Radziejewski with croton oil and with magnesium sulphate, as well as by Schiff[4] with aloes, jalap, and sodium sulphate. In all cases the results were the same as those already noted as obtained by Thiry. Carrying his investigations still further, Radziejewski, by forming intestinal fistulæ at such positions as would enable him to study the rate of passage of the intestinal contents, found that after a dog is fed upon flesh the small intestine empties the partially digested food into the colon so rapidly and in such quantity as to constitute, so to speak, a normal diarrhœa, and that the long delay in the exit and the hardening of the fæces occur in the large intestine. The liquid which passed into

* *Comptes-Rendus*, 1868, lxvi.; also Asp (*Ludwig's Arbeiten*, 1868).

the ascending colon agreed in all its characteristics with the stools of purgation. Radziejewski also asserts that he has established by direct experimentation that the peristaltic movements of the small intestine are affected very decidedly by drastics, and to some degree by Epsom salt, and that in all cases the large intestine is still more intensely acted upon. Although these experiments are very interesting, it cannot be allowed that they prove what is affirmed of them,—namely, that purgatives cause no increase of intestinal secretion, but only of peristaltic action. So much violence to natural conditions is done in the experiments after the method of Thiry that they seem to have very little weight. The assertion of Radziejewski, that croton oil confined in a loop of intestine is not absorbed, is a pure assumption, and his experiment does not warrant the conclusions drawn from it. The most that can be claimed is that these various researches show that increased peristalsis, especially of the large bowel, plays a more important *rôle* in the production of diarrhœa.

The fact that previous section of the par vagum prevents the action of purgatives* is opposed to the German theory, since it is almost certain that division of the nerves of the neck does not arrest peristaltic movements. Further, Armand Moreau[5] has found that a solution of Epsom salt placed in a knuckle of intestine isolated by means of two ligatures does cause a serous exudation into it, and in repeating M. Thiry's[6] experiments he has obtained opposite results. His experiments indicate three possible sources of fallacy in the work of the previous investigators: first, if the Epsom salt be not kept in the intestine for a sufficient length of time (some hours), no transudation occurs; second, in some cases the inner end of the isolated piece of intestine fails to adhere, so that the opening is not obliterated, and the matters injected into the arrested *cul-de-sac* really pass into the peritoneal cavity; third, atrophy of the mucous membrane and glandular apparatus of the *cul-de-sac* often follows almost at once upon the operation, and of course necessitates a negative result in the subsequent experiments. Lauder Brunton,[7] in a communication to the Medical Society of London, states that he has repeated Moreau's experiments, and found that magnesium sulphate injected into the intestine of a cat caused about two-thirds of a drachm of fluid to be secreted in four hours by each inch of the bowel operated on, although the proportion of sulphate was only one grain to an inch. In further experiments by Brunton,[8] gamboge, elaterium, and croton oil gave results similar to those of the Epsom salt. Vulpian[9] has also repeated the experiments of Moreau, and found that both magnesium sulphate and jalap provoke a "true intestinal catarrh," the vegetable cathartic at the same time increasing the peristaltic action, but the saline having no such effect. The experiments of Legros[10] and of M. Van Braam Houckgeest[11] show that salines do not increase the activity of the peristaltic movements, whilst those of Matthew Hay[12] are thought by him to prove that a saline purgative always excites more or less secretion from the alimentary canal, depending on the amount of the salt and the strength of its solution, and varying with the nature of the salt. To all this evidence may be added the experiments of Arthur Clopatt,[13] in which various purgative drugs thrown into the gut failed to increase the pressure in a manometer which had been introduced into a loop of the intestines tied at both ends, showing that they did not increase the intestinal contraction; and also those of Hess,† made by introducing into the duodenum, through a gastric fistula, a disten-

* See paper by H. C. Wood (*American Journal of the Medical Sciences*, 1870, lx).

† Hess also states that when, by the blowing up of the ball in the intestine, sodium sulphate, castor oil, calomel, senna leaves, croton oil, and colocynth were prevented from passing into the lower intestine, they failed to purge, although when introduced below the obstructing ball by a narrow tube running through it they at once caused diarrhœa. These experiments, if confirmed, would prove that the purgatives mentioned must come in direct contact with the lower part of the small intestine to produce liquid stools.

sible ball, which could be blown up by the long tube attached to it so as to fill the intestine, and noticing the rate at which the ball moved under the influence of a peristaltic movement. In these experiments it was found that hydragogues like senna affected very slightly the peristalsis, whilst drastics like croton oil had a very distinct influence.

The experimental evidence is very far from demonstrating that increased peristalsis is the cause of the watery stools produced by purgatives. The evidence, both experimental and clinical, is indeed overwhelmingly in favor of increased secretion. The facts proved by clinical observations and by experiment—that purgatives increase greatly the secretion in an isolated knuckle of intestine, that various purgatives act when taken into the blood, and that in these cases elimination by the bowels occurs ; that at least some purgatives (Headland[14]), when given by the mouth, are absorbed, disappearing from the alimentary canal and reappearing when purgation occurs ; that the stools induced by overdoses of various drastics, as elaterium, are so enormous as to cause the profoundest depression, and even choleraic collapse, in a very few hours ; that the discharges caused by hydragogues contain a large percentage of soda, the alkali of the serum ; that the relief obtained in portal congestion by the depletion of salines is very marked—are, when viewed together, incompatible with any other belief than that purgatives cause both increased secretion and increased peristalsis in the alimentary canal.

The question of the action of drugs upon the flow of bile is a very important one, the evidence concerning which is best considered under two headings : first, the experimental ; second, the clinical.

The experiments upon this subject which have attracted most attention are those of Scott, and of the Edinburgh committee, of which Bennett was chairman and Rutherford and Gamgee the workers. The method employed both by Scott and by the Edinburgh committee was to make biliary fistulæ in dogs in the usual physiological manner, and, after recovery from the operation had taken place and the bile regularly escaped by the external orifice, to administer the drugs, especially calomel and podophyllin, and study the effects upon the excretion of bile. Of the accuracy of their experiments we do not think that there can be any reasonable doubt. They prove that in dogs with biliary fistulæ mercury has no effect upon the flow of bile unless given in such quantities as to deteriorate the general health, when it diminishes the biliary secretion. The result does not, however, warrant the further conclusion that mercury does not increase the flow of bile in healthy dogs. The animals were in such an unnatural condition that, in spite of the daily ingestion of much more than the normal amount of food, they progressively emaciated, and finally died apparently of inanition : moreover, the innervation and probably also the blood-supply of the liver was very much interfered with. Under these circumstances it is clearly conceivable that the mercurial or other purgative might in the uninjured dog affect the biliary secretion, and yet fail to do so in the experiment, hindered by some obscure yet efficient cause. A. Röhrig[15] experimented by a method which simulated more closely the natural conditions, although even the results which he thus obtained do not seem to us conclusive. In curarized dogs in which life was maintained by artificial respiration, he placed a glass tube in

the gall-duct so that the bile could escape only through it. Under these circumstances, of course, after a time secretion ceased ; and Röhrig experimented not only on the effect of remedies upon the secretion while it was naturally going on, but also on their power of re-establishing it. He found that large doses of croton oil (eighteen drops) thrown into the duodenum caused an immediate very great increase, or a re-establishment, of the secretion. After the oil, the vegetable cathartics were most active, decreasing in power in the following order : colocynth, jalap and aloes, rhubarb and senna. Castor oil had very little influence, as had also the bitter salts. Calomel, even in large doses (twenty grains), very rarely re-established the secretion, but its power of increasing and maintaining it beyond the natural time for cessation was very marked.

W. Rutherford [16] used the method of Röhrig with some improvements. The drug, mixed with bile to facilitate absorption, was injected directly into the duodenum by means of a hypodermic syringe. The results obtained may be briefly summarized as follows :

Croton Oil in enormous doses neither purged nor affected the biliary secretion.

Podophyllin very greatly increased biliary secretion, especially when in such small doses that it did not purge severely.

Aloes very greatly increased biliary secretion, the doses used not purging greatly.

Rhubarb, *Colchicum*, *Iridin*, *Colocynth*, *Jalap*, *Sodium Sulphate*, *Sodium Phosphate*, and *Rochelle Salt* very greatly increased biliary secretion, at the same time purging.

Senna, *Taraxacum*, *Scammony*, *Gamboge*, *Castor Oil*, *Magnesium Sulphate*, and *Ammonium Chloride* acted very feebly, if at all, upon the liver.

Leptandrin, *Sodium Chloride*, and *Potassium Bicarbonate* had some, but not a powerful, effect on the liver.

Euonymin, *Sanguinarine*, and *Ipecacuanha* exerted a very powerful influence on the secretion of bile, and did not purge.

Calomel had no effect on the biliary secretion, but when to it a minute proportion of corrosive sublimate was added the effect was very marked ; *Corrosive Sublimate* acted as a very powerful biliary stimulant.

There is one objection to the experiments of Rutherford and Vignal entirely independent of the method employed,—*i.e.*, there were rarely more than two experiments with any one substance, and in several instances two experiments gave antagonistic results. It is very possible, indeed probable, that if a number of experiments had been made with each drug, the variation in results would have been much greater.

What is to be drawn from these various facts which have just been epitomized? Evidently but one conclusion,—that the experimental evidence at present does not warrant positive deductions as to the effect of purgatives upon the biliary secretion of healthy dogs. The canine diet and digestion are so different from the human that it is to be expected that medicines acting upon the digestive apparatus will influence dogs differently from man : thus, doses of elaterium that would kill a man can be given to some of the carnivora without causing the slightest purging. In view of these facts, the only fairly deducible conclusion in regard to the experimental evidence that has been brought forward is, that it must be received with the greatest reserve or be entirely laid aside when we desire to study the question as to the cholagogue action of remedies upon

man, and that our conclusions are most safely based upon clinical evidence.*

In regard to the drastics, there can be little doubt that almost any irritant purgative will to a greater or less extent increase the escape of bile, probably both by increasing its flow into the duodenum and by sweeping it out of the small intestine before absorption can take place. There are, however, two actively purgative substances of which it is especially asserted that they are cholagogues,—namely, calomel and podophyllin. The discussion of the action of these will be found under their respective headings.†

Violent purgation, whether produced by drugs, poison, or disease, has a distinct influence in checking the secretion of urine. In the experiments of Hugo Heinrichsen,[17] various vegetable cathartics affected the renal secretion much less than did salines, a result probably due to their being less actively hydragogue in their intestinal action. Heinrichsen further found that whilst the vegetable cathartics do not increase the solids of the urine, the salines have such influence; but in Matthew Hay's experiments the amount of the normal constituents of the urine was not found to be affected by the salt, and it is probable that the urinary solids are increased only by the weight of the eliminated saline.

Various divisions of purgative medicines have been proposed by different authors, but probably the most convenient arrangement is as follows:

1. *Laxatives.*—Medicines which simply unload the bowels, and are not able to cause active purgation, even when given in very large doses.

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* Rosenberg and Prevost and Binet have found that certain substances which are not purgative may be actively cholagogue upon dogs with permanent biliary fistulæ. The drugs may be arranged as follows:

GROUP I.—Substances augmenting greatly the flow of bile: oil of turpentine and its derivatives, potassium chloride, sodium benzoate and salicylate, salol, euonymin, muscarine.

GROUP II.—Substances slightly and inconstantly increasing bile: sodium bicarbonate and sulphate, sodium chloride, Carlsbad salts, propylamine, rhubarb, hydrastis.

GROUP III.—Substances lessening bile: potassium iodide, calomel, strychnine.

GROUP IV.—Substances without action upon the secretion of bile: sodium phosphate, lithium chloride, corrosive sublimate, arsenic, alcohol, ether, glycerin, quinine, caffeine, calumba, senna, pilocarpine, kairin.

† Rosenberg found that in dogs sodium salicylate increased the quantity and diminished the consistency of the bile; that turpentine had a slight stimulant power; whilst the Carlsbad salts seemed to increase rather than decrease the biliary flow. Neutral oils had a much greater power of stimulating biliary secretion than any other food or drugs, with the single exception of ox-gall. This is interesting in conjunction with the excellent results which are asserted to have been obtained in gall-stone and chronic *hepatic torpor* by the exhibition of from three to five ounces of olive oil after meals. In experiments upon a human being with a biliary fistula, William Bain (*Brit. Med. Journ.*, 1898, i.) reached the conclusion that Kissingen water, Carlsbad water, euonymin, sodium benzoate, and sodium salicylate increased both the amount of bile and of its solids, whilst podophyllin resin increased the elimination of solids without affecting the absolute quantity of the bile.

According to Stadelmann (*Bertiner klinische Wochenschrift*, 1896, 181) there are two cholagogues, the bile salts and the salicylates.

2. *Purges.*—Medicines which purge actively, but are not capable of acting as poisons, even in very large amount.

3. *Hydragogues* (including the *Salines*), which produce very large watery stools without much irritation. In overdoses, medicines of this class assume some of the characters of those of the next.

4. *Drastics*, which cause great irritation of the alimentary mucous membrane, and in overdoses are violent poisons.

It must be borne in mind that this classification is somewhat artificial; that the effects of the remedies depend much upon the doses in which they are administered, so that in sufficiently minute quantity a drastic may act as a laxative; and that the dividing lines between the groups are not distinct.

Enemata.—When it is desired simply to unload the lower bowels, the object can often advantageously be attained by injecting various materials into the rectum, so as, by mechanical distention or by irritating the mucous membrane, to stimulate the peristaltic action. The simplest, least irritant, and least active *enema* is one of cold water. In cases of habitual *constipation*, especially when complicated with *piles*, the injection of a pint of cold water at a fixed hour daily often acts most kindly. The ordinary "opening injection" consists of a pint of water and a tablespoonful, each, of salt, molasses, and soft soap; castor oil is often added to it, and, if it be desired to make it very active, a teaspoonful of oil of turpentine.

Large Enemata.—Except in individuals of extreme nervous irritability, there is little difficulty in filling the large intestine with water, and sometimes the fluid can even be made to enter the small intestine. The greatest gentleness should always be practised, a forcing syringe never being used. The apparatus should consist of a rectal tube, and an ordinary india-rubber tube, four feet long, fitted to the rectal tube and to a funnel, india-rubber bag, or other receptacle. The patient should lie upon his back with the hips elevated, or in the knee-chest position, so that the pelvis may be much higher than the shoulder. The rectal tube having been introduced into the rectum, the end with the receptacle containing water is to be raised vertically. It is essential that the tube be fitted with a cock, or be pinched, so as to regulate the passage of the liquid. In this way from five to nine pints are readily injected. Unless it is especially desired to get the effect of cold or heat upon the intestine, the water in the receptacle should be about 100° F.

Large enemata are especially valuable as affording a means of locally treating the intestines. Very frequently in *dyspepsia*, *chronic constipation*, and other functional diseases of the digestive organs, the large intestine habitually contains scybala, fecal matters, acrid secretion, or other irritant substances, whose removal two or three times a week by means of simple water or water impregnated with half a drachm of sodium bicarbonate to the quart brings great relief. In *dysentery*, chronic or acute, and in *pseudo-membranous colitis* or *enteritis*, by means of the large

enemata, local application can be made to the colonic mucous membrane. In this way, in acute *dysentery*, water, antiseptics, germicides, bismuth subnitrate, and other appropriate remedies can be used. In chronic dysentery, one drachm of silver nitrate dissolved in half a gallon of water is often of the greatest service.

As originally recommended by Mosler, these injections are sometimes very useful against intestinal parasites. In this way especially may they be used against the *oxyuris vermicularis*, which often inhabits the whole of the large intestine. In bad cases of *seat-worm* the large injection should always be employed. In obstinate cases of *tape-worm*, when the worm has been weakened, and partially or completely expelled from the small intestine under the influence of vermicides given by the mouth, filling the colon with a medicated solution often brings success. Sometimes a saturated solution of salt suffices, or quassia may be employed. Mosler records as especially effective a tablespoonful of chlorine water to every pint and a half of water. A. Röhrig[18] having found that intestinal injections of water have a very great influence over the secretion of bile, Mosler has been led to try forced enemata in *catarrhal* and other *jaundices*, with asserted good results.

Hypodermic Use of Purgatives.—Under many circumstances great advantage would be gained by having a purgative which could be used hypodermically; but, unfortunately, there is no known purge which lends itself favorably to this method of administration, most of them having no action when so given, and the few that are capable of action producing so much local disturbance as to forbid their employment except under the most pressing circumstances.

Fronmüller[19] says that one to three grains of Merck's aloin dissolved in hot water, administered hypodermically, act as an efficient purge; but R. Kohn[20] states that in his hands aloin of three different commercial varieties, hypodermically administered in ten times the dose employed by Fronmüller, failed to act. In 1881, as the result of an elaborate investigation, A. Hiller[21] reached the conclusion that whilst there are four purgatives—namely, aloin, cathartic acid, and the pure colocynthin and citrullin of Merck—which are capable of purging when given hypodermically, they are all too irritant for practical use; a conclusion which was confirmed by Kohlstock.[22]

According to Meyer, the irritant action of Barbadoes aloin is largely due to the precipitation in the subcutaneous tissue of insoluble and extremely irritating crystals of the drug, and may to a considerable extent be overcome by the use of formamide as a vehicle. Kohlstock affirms that aloin or cathartic acid acts much better when given by rectal injection than when administered hypodermically.*

* The following formulæ are recommended by Kohlstock for rectal use: Acid. cathartic. e senna, gr. iii; aq. dest., gr. vii; natr. bicarb. ad react. alkalin., q.s.—Colocynthin, gr. i; alcohol, gr. xii; glycerin, gr. xii.—Citrullin, gr. ii; alcohol, gr. xlix; glycerin, gr. xlix.—Aloin, gr. xv; formamide, ʒii. For rectal use a solution of aloin in glycerin may be substituted. Kohlstock gives the full purgative dose by the rectum as —aloin 15 grains; cathartic acid, 6 grains; colocynthin, 0.04 grain; citrullin, 0.02 grain.

The indications to fulfil which cathartics are used are as follows :

1. *To unload the Bowels.*—It is not necessary, in a work like the present, to say anything about the evil results of retained fecal matter, but only to point out the methods of relief. Before this can be done to advantage, however, a summary of the causes of *constipation* is required. Constipation may be well divided into acute and chronic. *Acute* or *temporary constipation* is that which occurs under special, transient circumstances, as in convalescence from acute disease, and in pregnancy. It is to be relieved by the use of laxative articles of diet, and, this not sufficing, by laxatives or purgative medicines. It should never be forgotten that acute constipation is sometimes due to organic affections of the alimentary canal, such as enteritis or intussusception, or is caused by mechanical obstacles, such as a hard foreign body or an enormous gall-stone. It is evident that such cases are not simple constipation,—that the treatment required is essentially different from that of the latter affection, and is various according to the lesion. For the diagnosis and treatment of these diseases the reader is referred to works on the practice of medicine. *Chronic constipation* may be due to sedentary habits of life ; to habitual overwork, especially of the nervous system ; to a deficiency of intestinal secretion and of peristalsis, apparently natural to the individual and without obvious cause ; to long-continued voluntary habit of restraining the desire to go to stool ; to lead or other forms of poisoning ; and to diseases of the nervous system producing a paralytic state of the intestinal muscular fibres. It is evident that in the treatment of these various forms of constipation due regard must be paid to the cause, which should always, if possible, be removed. There are also certain cardinal principles which apply to the treatment of all forms of chronic constipation. They are as follows :

A voluntary effort at defecation is to be daily made at a fixed hour, whether the desire exists or not.

Medicines are to be avoided as far as possible, a sustained effort being made to regulate the bowels by means of diet.

In very many cases the daily use of enemata of cold water, with attention to diet, suffices to attain the desired result.

If medicines become necessary, as small an amount as will suffice, and the mildest drugs, are to be used. Purgatives or laxatives are at best merely temporary devices, and if abused in costiveness increase the trouble. So far as can be, the attempt should be to produce a permanent impression, an alteration of the intestinal glandular action or peristalsis. Thus, when atony of the muscular coat exists, strychnine, or, according to comparatively recent experiments and clinical observations, Calabar bean, may be employed ; if the hepatic or other glands are habitually torpid, nitro-muriatic acid may be administered.

When constipation is attended by low spirits and a coated tongue, it is almost always due to a deficiency of secretion, and may be looked

upon as a form of dyspepsia : in such cases nitro-muriatic acid is especially valuable, but sometimes a mild mercurial course seems almost imperative.

A second use of cathartics under the present indication is to remove offending materials, as indigestible or irritant food, foreign bodies, acrid discharges, etc. In many cases of indigestion with undue fermentation in the alimentary canal a brisk cathartic does great good by producing the expulsion of micro-organisms. The possible importance of this is shown by the experiments of Gilbert and Dominici,[23] who found that a single dose of a saline caused in a healthy man the expulsion of over four hundred and eleven billion organisms.

2. *To deplete.*—On account of the large serous flow which they produce, the hydragogue cathartics when freely exhibited cause a very decided general depletion.

Local depletion by means of cathartics is called for in *congestion of the portal circulation*, as well as in *dysentery* and other acute intestinal inflammations. Under the first of these conditions may, we think, be included without violence cases of so-called *torpidity of the liver*, which will be discussed in the article upon calomel. In acute *intestinal inflammations* the salines are to be preferred when depletion is desired, as they produce large serous discharges and are not irritant.

3. *To promote Absorption.*—By emptying the blood-vessels the cathartics favor the absorption of the exuded fluid in general dropsy. For this purpose the hydragogues, and especially elaterium, are the best purgatives. The production of catharsis is the surest method of relief in general *dropsy*, also in *ascites;* in other forms of local effusion its effects are less marked. As, however, purgation is the most exhausting of all the plans employed for the cure of dropsy, due regard must always be had to the strength of the patient. It is frequently necessary actively to support or even to stimulate while it is being carried out.

4. *To revulse.*—The long tract of the alimentary canal affords a great extent of surface upon which to practise revulsion in certain brain diseases, as in *mania* and rheumatic or gouty *irritation of the cerebrum*. In *hyperæmia* of the brain, purgatives do good by depleting as well as by acting as revulsives. The drastics should be preferred.

5. *To eliminate.*—It cannot be doubted that the use of purgatives in such diseases as fevers and cholera, with the idea of eliminating some *materies morbi*, rests simply upon a crude, unproved, and probably false pathology. In *rheumatic disease* and in *gout* it is more probable that they do good in this way, although it is by no means certain that the advantage derived from their use is not simply due to depletion. In cases of retained renal secretion, the evidence is very decided that they do aid in expelling the products of retrograde metamorphosis.

LAXATIVES.

As has been already stated, constipation should always, when possible, be overcome by laxative food. There are two qualities by virtue of which food is laxative. Chief of these is *bulk*. All aliment which contains a large amount of innutritious material affords a large residuum, which, by distending the intestine, stimulates peristalsis. Contrariwise, articles of diet which are highly nutritious and afford but little residuum are constipating. This holds good, more or less strictly, among the lower animals. Thus, the flesh-eating carnivora are habitually constipated, the grass-eating herbivora very generally lax.

Owing to its containing so little of the innutritious portion of the grain, the finest white flour favors a costive habit, while the "cracked wheat," in which the whole grain is eaten, is laxative,—as to a still greater degree is bran, which is composed almost wholly of the husk of the wheat, the least nutritious portion of it, and therefore leaves a large residuum after digestion. *Cracked wheat* is boiled into a sort of jelly-like mass, and eaten with cream and sugar, while *bran* is taken in the form of bran bread, bran crackers, or bran mush. *Unbolted flour*, containing the whole of the grain, is about equal to cracked wheat, and is often made into bread. *Indian meal*, in the form of cakes or of mush, is highly nutritious and somewhat laxative; *oatmeal* is decidedly laxative, scarcely so much so as bran, but much more nutritious. When it agrees with the stomach, and is digested, it is probably the best of all these laxative articles of food. As the oats produced in southern climates are very inferior, care should be taken to procure oatmeal manufactured from Northern grain. It should be thoroughly cooked, and is best eaten in the form of a thick porridge. In dyspepsia all of these articles sometimes disagree with the stomach and cannot be used.

Some dietary articles seemingly possess *dynamic* laxative powers,—*i.e.*, they exert a direct action which is not mechanical, but is similar to, although far less active than, that of the true purgatives. They intensify the intestinal action. Chief among substances of this class are *molasses* (SYRUPUS FUSCUS) and it scongener, *brown sugar; white sugar* (SACCHARUM, U. S.) probably does not share these laxative powers; *sugar of milk* (SACCHARUM LACTIS, U. S.) is probably also nearly inert. Of course, great care is usually necessary in taking advantage of the laxative virtue of molasses, on account of the danger of producing fermentation and acidity in the primæ viæ.

There are certain foods which combine the two methods of action spoken of. Chief among these are the fresh acidulous fruits—such as apples, pears, etc.—and the dried fruits. Of the latter, the fig (FICUS, U. S.) is one of the most palatable, and, owing probably to the great number of small seeds which it contains, is the most efficient. Prunes, U. S., are as agreeable as figs. To a limited extent the finest varieties of them may be eaten raw; but they are especially to be recommended stewed. When it is necessary, a pinch of senna-leaves may be cooked with them, so as to increase their activity without affecting their flavor.

Among constipating articles of diet, it is only necessary to call attention to milk as one of the most decided of the class.

MANNA—MANNA. U. S.

An exudation of the European ash, Fraxinus Ornus, chiefly produced in Sicily and Calabria. The best quality, *flake manna*, occurs in unequal, rough, stalactite-like pieces with a crystalline or granular fracture. Manna has a slight odor, a sweet, mawkish taste, and should contain from forty to eighty per cent. of the saccharine, active, crystalline principle, *mannite*, which differs from ordinary sugar in not containing equal parts of hydrogen and oxygen, and is therefore not readily convertible into grape sugar or its derivative, alcohol. It is a gentle laxative, in large doses sometimes causing flatulence and pain; rarely used by itself, it is often added to purgative infusions. The laxative dose for an adult is half an ounce to two ounces (15–60 Gm.); for a child, one to four drachms (4–15 Gm.) in an aromatic infusion.

CASSIA FISTULA. U. S.—*Purging Cassia* is the dark, sweetish, acidulous pulp of a hard, blackish, cylindrical pod produced by Cassia Fistula, a tree of Egypt and India. It may be used as a laxative in doses of half an ounce (15 Gm.), but is apt to cause griping. It enters into the official confection of senna.

FRANGULA. U. S.—The bark of Rhamnus frangula, one of the buckthorns of Europe, is considerably used abroad as a laxative. Its active principle is a glucoside, *frangulin;* a fluid extract (EXTRACTUM FRANGULÆ FLUIDUM, U. S.) is official,—dose, ten to twenty minims (0.6–1.2 C.c.). In this country it is employed very rarely, but the bark of Rhamnus Purshiana, or California buckthorn, is very largely used under the name of *Cascara Sagrada* (RHAMNUS PURSHIANA, U. S.). It contains a glucoside, *purshianin*, closely allied to frangulin, and often acts most happily as a laxative in *habitual constipation.* Fifteen drops (1 C.c.) of the fluid extract (EXTRACTUM RHAMNI PURSHIANÆ FLUIDUM, U. S.) may be given one or two hours after meals, or half a fluidrachm (2 C.c.) may be administered at bedtime. The solid extract, although not official, is effective in doses of two to five grains (0.13–0.3 Gm.).

EUONYMUS, U. S., or *Wahoo*, the bark of Euonymus atropurpureus, was found by Noel Paton,[24] when given to dogs in small dose, to increase greatly the elimination of urea and uric acid, and by Rutherford to be in large dose an active cholagogue in dogs. In man its effects are often most happy in cases of *habitual constipation* and *hepatic torpor.* It acts very slowly and purges only moderately. The dose of the fluid extract is a dessert- to a tablespoonful (8–15 C.c.); of its resinoid extract, *euonymin* (the best preparation), two to four grains (0.13–0.26 Gm.): in cases of *dyspepsia* it may be repeated with good results two or three times a week.

TAMARINDUS — *Tamarind.* U. S. — The preserved pulp of the fruit of Tamarindus Indica, a large tree, native of the East and West Indies. In the market it occurs as adhesive masses composed of pulp, membranes, strings, and seeds, and having a sweet acidulous taste. It contains a good deal of citric acid, much less tartaric acid, and a little malic acid. It is rarely used at present, but is laxative in doses of half an ounce to an ounce or more, being eaten like preserves, and enters into the confection of senna.

MAGNESIA—LIGHT MAGNESIA. U.S.
MAGNESIA PONDEROSA—HEAVY MAGNESIA. U.S.

The *heavy* and the *light* magnesia differ only in their physical characters, the particles being differently aggregated. Magnesium carbonate (MAGNESII CARBONAS, U. S.) is manufactured by precipitating a solution of magnesium sulphate by one of sodium carbonate. If the two solutions be concentrated, the dense or heavy carbonate will fall; on the other hand, if the solutions be dilute, the precipitate will be a light carbonate. Heavy magnesia is obtained by calcining a heavy carbonate; light magnesia, by using a light carbonate. All of these substances are of a milk-white color, and occur in powder; the carbonates sometimes in very light cubical blocks. They are all practically insoluble in water, freely soluble in dilute acid, and in the presence of acids they all act as alkalies.

THERAPEUTICS.—Magnesia and its carbonate are antacid and laxative. For their purgative powers they are probably dependent upon the presence of acids in the primæ viæ, and hence their effects vary. When taken repeatedly they are said at times to accumulate in the intestines, and should not be used as an habitual laxative. They are often given along with Epsom salt or senna, on account of their antacid properties. Their chief use is in acute *acid dyspepsia*, in *sick headache*, in *diarrhœa* with excessive acidity in children, in *gout*, in *rheumatism*, and in various *cutaneous affections*,—wherever, in a word, a laxative antacid is indicated. Dose, one drachm to half an ounce (4–15 Gm.); for a child a year old, from five to twenty-five grains (0.3–1.6 Gm.), according to the effect desired.

SULPHUR.

Sulphur is official in three forms: SULPHUR SUBLIMATUM, or *Sublimed Sulphur;* SULPHUR LOTUM, or *Washed Sulphur;* and SULPHUR PRÆCIPITATUM, or *Precipitated Sulphur.* The first of these is made by subliming sulphur into cool chambers, and always contains some sulphuric acid, generated during the process. When freed from the acid by washing with warm water and ammonia, it constitutes the washed sulphur. The U. S. Pharmacopœia directs the precipitated sulphur to be prepared by boiling lime and sulphur together, so as to form calcium sulphide, and precipitating this with hydrochloric acid.

The sublimed and the washed sulphur occur as sulphur-yellow, crystalline powders; the precipitated as a whitish powder, whose particles are often coherent into friable lumps. For an account of the various allotropic forms of sulphur, and its chemical properties, the reader is referred to works on chemistry. It is insoluble in water, but soluble in alkaline solutions, alcohol, the fixed and volatile oils, chloroform, ether, etc.

PHYSIOLOGICAL ACTION.—When applied locally, sulphur is almost without influence. Taken internally, it is dissolved to some extent in the alkaline intestinal juices and absorbed. It has been detected in the milk, sweat, urine, and even in the breath. It would appear to suffer oxidation in the system; at least its ingestion is followed by increase of the urinary sulphuric acid (Regensburger[25]). When in sufficient quantity, sulphur acts as a mild laxative, producing soft, semi-liquid, feculent stools, accompanied generally by much offensive flatus of sulphuretted hydrogen. It is affirmed that in some instances the latter gas has been so freely generated and absorbed as to cause systemic poisoning. Cases have also been reported in which the flowers of sulphur acted as an irritant poison; but this, without doubt, has been owing to their containing a large quantity of sulphuric acid. Its continued use has probably some effect upon nutrition; the secretions generally are slightly increased, and some have affirmed that the temperature is somewhat elevated; but the truth of this is certainly very doubtful. The results of clinical experience indicate that it has an especial tendency to act upon the skin and mucous membranes.

THERAPEUTICS.—As an habitual laxative, sulphur has been used with asserted advantage in cases of *hemorrhoids* and of chronic *rheumatism*. In subjects of the latter disease it is affirmed that it exerts a beneficial alterative influence, especially in *sciatica* and in *lumbago* and other varieties of *muscular rheumatism*. It has also been employed as an alterative in various cutaneous affections; and in the form of natural sulphur-waters, used externally and internally, there is much testimony as to its value in both rheumatic and *skin diseases*. It is affirmed by Doit[26] that the natural sulphur-waters are of very great value in the treatment of chronic *syphilis*, as they undoubtedly are in chronic *gout* and *rheumatism*. They may be substituted by the artificial sulphur-water described under the heading of EXPECTORANTS. Sulphur is very largely used as a parasiticide in cases of *itch*.

Tilbury Fox recommends its application in the following manner. He says, "I have applied to *all papules and vesicles* the following ointment: sulphur, half a drachm; ammonio-chloride of mercury, four grains; creosote, four drops; oil of chamomile, ten drops; and an ounce of lard. This is rubbed in night and morning for three days, especially to the interdigits and wrists; the same shirt is kept on till the third day, when it is changed and a warm bath given. The use of the parasiticide for two or three days should be followed by a good washing and the discontinuance of the remedy for a night. If the patient be not troubled with itching during the night, we may conclude that the acari are killed, and all we need to do is to guard against the hatching out of fresh acari by the light application of our

parasiticide once a day to any 'pimply' or itchy place for a few days longer, taking care that the foul clothes are well heated or scalded. 'Not too strong and not too long' is my rule in the use of remedies for scabies. The occurrence of red, rough, erythematous patches is a sign that the remedy itself is creating a disease."

ADMINISTRATION.—Sulphur is generally given in powder, mixed with syrup or molasses. Dose, as an alterative, ten to twenty grains (0.6–1.2 Gm.) three times a day; as a laxative, one to three drachms (4–11 C.c.) at bedtime.

POTASSA SULPHURATA. U. S.—*Sulphurated Potassa* is prepared by heating together sulphur and potassium carbonate. It occurs in liver-brown fragments, which form an orange-yellow solution in water. Its taste is acrid, alkaline, and very disagreeable. When moistened, it feebly emits the odor of hydrogen sulphide.

Locally applied, the potassium sulphuret is a very decided irritant. Taken in large quantities, it is a violent corrosive poison, and is said to have produced fatal gastro-intestinal inflammation. In medicine it is chiefly employed externally. It has been used as a stimulating ointment (half a drachm to an ounce) in various skin affections, and is also used for the formation of sulphur baths, the strength of which should vary, according to the requirements of special cases, from two to six ounces of the drug in thirty gallons of water. They should be taken warm, the patient remaining in from twenty minutes to two hours, and are said to cause a general excitement, amounting in some susceptible persons to high fever. When employed strong, they sometimes occasion a papular eruption. They have been used in *chronic rheumatism* and in various *scaly skin diseases.*

CALX SULPHURATA. U. S.—*Sulphurated Lime.*—The original recommendation by Sydney Ringer[27] of the *calcium sulphide* in frequently repeated doses of a tenth of a grain (0.006 Gm.) in *boils* when they appear in successive crops, and in various *scrofulous* and other unhealthy *sores*, such as occur especially in children, also in scrofulous *glandular enlargements*, has been confirmed by Duhring and others. The drug is often given in half-grain (0.03 Gm.) doses. The Calx Sulphurata of the Pharmacopœia contains not more than thirty-six per cent. of pure calcium sulphide, but is the commercial article known by that name.

PURGES.

OLEUM RICINI—CASTOR OIL. U.S.

A fixed, nearly odorless oil, of a nauseous taste, obtained from the seeds of Ricinus communis by expression. The seeds are slightly warmed before being put under pressure, so as to liquefy their contained oil; and the crude oil obtained from them is boiled with a small

amount of water, so as to coagulate its albuminous impurities. Castor oil is remarkable for being soluble not only in ether, but also in alcohol. The *castor-oil seeds*, or *beans*, as they are commonly called, contain an acrid, violently poisonous principle, *Ricin*.*

PHYSIOLOGICAL ACTION.—Castor oil acts upon the human organism as a mild but decided purgative, producing copious fluid fecal discharges, and in overdoses sometimes vomiting, and always purging freely. The bulk of the castor oil is *ricinolein*, a glyceride of *ricinoleic acid*, which appears to be the purgative principle, and to be absorbed ; at least Canvane† affirms that in children castor oil sometimes purges when rubbed upon the skin of the abdomen, and when taken into the stomach it has been known to exude from the skin.‡ Buchheim,[28] although he submitted the passages produced by the oil to careful chemical manipulation, failed to detect it or any derivatives. According to the experiment (quoted by Stillé) of Hale upon himself, half an ounce of castor oil injected into a vein produces malaise, nausea, faintness, anxiety, and general dulness and depression, without purging.

THERAPEUTICS.—On account of the mildness of its action and a special property of soothing an irritated bowel, castor oil is constantly employed whenever it is desired simply to evacuate the intestinal canal ; not so much, however, in *chronic constipation* as when a temporary action is alone required. In various inflammatory or irritative affections of the alimentary canal, castor oil is often of the greatest service. This is especially seen in the acute *diarrhœas* and even in the *chronic enteritis* of children, but also holds good in the *diarrhœas* and *dysenteries* of adults. In *chronic pseudo-membranous colitis* we have seen very excellent results from the long-continued daily use of the oil.

The application of the fresh leaves to the breasts, combined with the administration, three times a day, of a teaspoonful of a fluid extract of the leaves, is said to decidedly increase the secretion of milk. The dose of the oil is half an ounce to an ounce (15–30 C.c.) for an adult ; for an infant a year old, one to two teaspoonfuls (4–7 C.c.). In dysentery it is sometimes advantageous to give the drug in small dose every three hours until a decided purgative operation is induced.

The repulsive taste of castor oil will sometimes cause vomiting ; the oil should, therefore, be given in soft capsules, or in some way disguised, as in strongly aromatized water, or in emulsion. A mixture of

* Three beans have caused death in the adult. The symptoms, which do not usually come on until from two to five hours, are severe abdominal pain, violent vomiting and purging, which after a time may become bloody, collapse, severe muscular cramps, cold sweating skin, contracted features, thirst, restlessness, and small rapid pulse. After death, intense redness and even abrasion of the stomach and of the small intestine are found. After the stomach and large intestine have been thoroughly washed out with warm water, the treatment of castor bean poisoning is that of toxic gastro-enteritis,—namely, the use of opium, leeches, ice, demulcent drinks, counter-irritation, etc. See Kobert and Stillmark (*Arbeiten Pharmak. Inst. zu Dorpat*, iii.).

† See H. Meyer (*Arch. f. Exper. Pathol. u. Pharm.*, 1890, xxviii.).

‡ Ward's case (*London Med. Gaz.*, x. 377).

equal parts of glycerin and castor oil, with two to four drops of the oil of cloves or cinnamon to the fluidounce, is readily taken by most persons; especially if it be given in an ice-cold spoon, which chills it into a viscid mass.

HYDRARGYRUM. U.S.

The only preparations of mercury which are used as purgatives are *calomel* and *blue mass*. Of these the first is by far the more active, and indeed is the only one which can be relied upon to purge.

The chief interest in the purgative action of mercurials centres in the question as to their influence upon the liver. The evidence at present derivable from experiments upon the lower animals has already been discussed, and the decision arrived at that it must be rejected.*

When calomel is given to a healthy man in moderate purgative doses, green liquid stools are produced, which, after larger doses, are replaced by brown passages. The color of these passages has always been supposed by clinicians to be due to the presence of bile; but recently it has been affirmed that the green tint is owing to a compound of the mercury itself. Although no chemical proof of the presence of the metal or its salt has, that we are aware of, been furnished, yet it can scarcely be doubted that mercury is present in the first passages produced by calomel.

The question, evidently, is not, Is mercury ever present in the green stools? but, Is it always present? or, in other words, Is it an integrant portion of them? The evidence is not so abundant upon this point as is desirable, yet seems sufficient to furnish a negative answer to the last question. Simon[29] and Golding Bird,[30] in careful analyses, both failed to detect the metal; and, as the recognition of mercury is an exceedingly simple chemical problem, it seems impossible that these chemists could have overlooked the metal if it had been present. Simon's analysis was performed upon the fifth stool after the administration of a large dose of calomel. The passage was fluid, perfectly green, had no fecal odor, exhibited a mild acid reaction, and showed under the microscope a great number of mucus-corpuscles and epithelium-cells. Ether extracted from the solid residue (obtained by evaporation) a considerable amount of fat, which had an acid reaction, contained cholesterin, and was colored by biliverdin. All the other substances which were separated from the stool by water and alcohol were more or less colored by bile-pigment. Bilin, bilifellinic acid, and biliverdin were found in large quantity.

The most satisfactory evidence is, however, that furnished by Michéa,[31] who examined chemically the fæces under four different conditions. First, the spontaneous dejections of six healthy individuals: no bile was detected. Secondly, green stools of three persons suffering from gastro-intestinal derangement: bile-pigment was found in one case only, and in that could not be detected after persistent vomiting had ceased. Thirdly, calomel having been given to eight healthy persons, five men and three women, bile was readily demonstrated in the green passages produced in all of the subjects. Fourthly, saline and resinous purgatives were given to five persons, but no bile could be detected in the liquid stools.

To the evidence brought forward in favor of the proposition that calomel given

* For a very elaborate review of the clinical evidence, see Thomas R. Fraser's paper in the *Edinb. Med. Journ.*, April, 1871.

to healthy men causes an increased escape of bile from the alimentary canal may be added the conclusive fact that in some persons, whose idiosyncrasies render them very susceptible to the action of calomel, it produces not merely purging, but also vomiting of bile, which is scarcely at all altered.

From the facts which have just been passed in review, the conclusion seems inevitable that mercurial purgatives given to healthy persons cause the escape of large quantities of bile from the alimentary canal.*

As is well known, when from any cause bile does not pass into the duodenum, the stools become very pale, of a peculiar potter's-clay, or even white, color. Very frequently under these circumstances, which may coexist either with diarrhœa or with constipation, mercurials will modify the color of the passages and alleviate or cure any symptoms present. In many cases the mercurials are, of course, powerless to effect the desired result; but this depends upon the cause being organic, or of some other nature not to be overcome by a secretory stimulant.

As mercurials in health increase the flow of bile from the intestine, and as they will sometimes re-establish it in disease when the secretion has altogether ceased or has been very materially diminished, the conclusion seems inevitable that mercurials have the power of directly or indirectly increasing the secretion of bile. The only objection of any force to be urged against this deduction is founded upon the idea that the drug simply increases peristalsis in such a way as to cause the bile naturally in the duodenum to be swept out instead of being absorbed. The answer to this is embraced in the following facts: mercurials often restore the color of the passages when pale from arrested secretion, often without producing diarrhœa; other even more active purgatives fail to induce the same bilious passages; when diarrhœa exists with clayey stools, the change in the color of the passages caused by a mercurial may coincide with an unincreased, or even a lessened, amount of liquidity; diarrhœa ordinarily does not cause bile to appear in the passages.

THERAPEUTICS.—A mercurial purge is especially indicated by the congeries of symptoms known as *biliousness:* a heavily coated tongue, bitter, disagreeable taste, severe headache, depression of spirits, loss of appetite, slight nausea, and light-colored passages. It should be borne in mind that one or several of these symptoms may be absent in any individual case. Of all single indications for the use of calomel, the occurrence of *potter's-clay-colored* passages is the most important; and if such stools exist, and do not depend upon an organic cause, repeated small doses of the mercurial should be given, whether there be constipation or diarrhœa.

In *bilious fever,—i.e., malarial fever with congestion of the liver,*—a

* J. Zawadzky (*Vratch*, 1887, abstracted, *Bull. Thérap.*, 1887), as the result of his own researches, comes to the improbable conclusion that the presence of bile in the stools as the result of the use of calomel is due to the antiseptic property of the mercurial, the bilirubin being converted into biliverdin, which is prevented from undergoing decomposition.

mercurial purge, or several mild mercurial purges, will often, by exciting the action of the hepatic gland, be of great service in preparing the way for or aiding in the action of quinine. In *catarrhal jaundice*, mercurials, on the whole, offer, we think, the most frequently successful mode of treatment. It is evident that in such cases calomel does good not merely by its cholagogue influence, but even to a greater extent by its antiphlogistic power, no doubt lessening the viscidity of the secretions and abating the inflammatory action in the hepatic ducts. In many instances it is well to exhibit the mercurial in purgative doses to start with; but the main reliance is to be placed in the continuous exhibition of small doses of the drug until the gums are rendered slightly sore. Anything like profuse salivation is, of course, to be avoided. In *dysentery* of an acute sthenic type, calomel acts as an antiphlogistic and as an alterative, not only to the liver, but to all the intestinal glands. It is possible that it acts also as a bactericide, since N. P. Wassilieff[32] has found that although it has no effect in checking the action of the digestive ferments, it has a very pronounced influence in stopping putrefactive changes in food by killing the organisms which produce such changes.

RHEUM—RHUBARB. U.S.

The root of Rheum officinale, Baillon, and other species of Rheum growing in China, Chinese Tartary, and Tartary.

Rhubarb occurs in hard, irregularly cylindrical or roundish pieces, of a brownish-yellow color and peculiar bitter taste, and imparting to the teeth a sense of grittiness, due to the presence of great numbers of minute crystals of calcium oxalate. At one time rhubarb was cultivated to a considerable extent in Europe, but *European Rhubarb* is no longer found in our markets.

Rhubarb contains, besides a peculiar tannic acid, *chrysophanic acid*,*

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* Under the names of *Goa Powder* and of *Araroba* or *Chrysaroba* have long been used in Brazil and the East Indies certain powders, varying from fine to coarse and from a light yellow to a dark chocolate, which are now known to be identical, and the product of a Brazilian tree. They depend for their activity upon *chrysarobin*, of which, according to Squier, they often contain as much as sixty-five per cent. Chrysarobin was formerly supposed to be identical with chrysophanic acid, but is a distinct principle. When taken internally in doses of from six to eight grains, it produces in about four hours repeated vomiting, sometimes followed by purging (I. A. Thompson, *Brit. Med. Journ.*, 1887), and it has been shown by Weyl to be an active irritant poison. It must not be confounded with *anthrarobin*, a distinct substance produced by Liebermann from alizarin (*Ber. d. Chem. Ges.*, 1888), which Weyl (*Arch. f. d. Ges. Phys.*, 1888, xliii.) has proved to be free from poisonous properties. The only practical application of the Goa powder or its active principle is in certain *skin diseases*, especially in *psoriasis*. According to the researches of Balmanno Squier, its power in this disorder is extraordinary. He uses an ointment made by dissolving the acid in hot lard (five grains to two drachms in one ounce), cooling, and mixing thoroughly with a pestle. The ointment sometimes produces excessive irritation; hence it is advised to commence with a strength of not more than twenty grains to the ounce, well rubbed in twice daily. The acid stains of a dark purple; this can be removed from hair, underclothes, etc., by hot benzole, if no soap or alkali has been used. The skin and nails are said to contain enough potash to set the dye.

emodin,* and probably a third active substance, *rhein*, of Hesse. *Rhein* and *rhabarbarin*, of the older chemists, were complex bodies.

PHYSIOLOGICAL ACTION.—Rhubarb is somewhat stomachic, tonic, actively purgative, and, owing to its tannic acid, secondarily astringent, leaving a decided tendency to constipation after the primary purgation. Owing probably to its chrysophanic acid, it gives a yellowish color to the milk of nursing women and to the urine. Rhubarb urine is to be distinguished from that of jaundice by its becoming purplish-red on the addition of an alkali. Rhubarb is asserted to affect chiefly the muscular coat of the bowels, and to purge by increasing peristalsis; but we have never met with any proof of this common belief.

THERAPEUTICS.—Notwithstanding its astringent property, rhubarb is largely used as an habitual laxative, because it does not impair, but, on the contrary, seems to strengthen, the appetite and the digestion. It should not be used in a high sthenic state of the system, or when depletion is necessary, but is very valuable when it is desired simply to unload the bowels in a debilitated subject. It is much used in *diarrhœa*, with intestinal weakness or relaxation, to unload the bowels of acrid secretions. The *aromatic syrup* combined with an alkali is especially serviceable in the *summer bowel-complaints* of children when the stools are greenish and mucous.

ADMINISTRATION.—Rhubarb is seldom employed in powder, but, when used, may be given in the dose of twenty grains (1.2 Gm.). In chronic constipation, small pieces of the root are very often carried in the pocket and chewed by the person affected *pro re nata*. The U. S. Pharmacopœia recognizes the following preparations: EXTRACTUM RHEI,—dose, five to ten grains (0.3–0.6 Gm.); PILULÆ RHEI, each containing three grains of rhubarb; PILULÆ RHEI COMPOSITÆ (two grains of rhubarb, one and a half grains of aloes),—dose, two to four pills; PULVIS RHEI COMPOSITUS (rhubarb and magnesia),—dose, half a drachm to a drachm (2–4 C.c.); EXTRACTUM RHEI FLUIDUM,—dose, twenty to

* *Emodin.*—The nature of the active principles of many of the vegetable purgatives is still obscure. Several of them—namely, rhubarb, senna, aloes, frangulin, and cascara sagrada—are believed by some chemists to owe their properties to the presence of *anthracene* compounds. Such compounds are usually glucosides. Of these compounds attention has been recently especially drawn by Tschirch to *emodin* (*trioxymethylanthraquinone*), as being the real active principle of the class. The great difficulty is to tell how far a principle obtained by chemists from one of these drugs originally exists in the drug and how far it has been formed by the decomposition of some other principle. Thus, chemists of repute affirm that emodin is a decomposition product from frangulin; whilst Tschirch believes that many of the drugs named owe their great activity to the presence in them of substances produced by the decomposition or change in emodin.

Emodin has been used to some extent as a laxative in doses of one to two grains. In view of the fact that there is only two per cent. of aloe-emodin in Barbadoes aloes, about two per cent. of rhubarb-emodin in rhubarb, and in senna a still smaller percentage of emodin, it seems certain that emodin does not fully represent the various drugs. The experiments of Asher, upon which Tschirch based the theory that in the emodin group the irritation is caused by the local stimulation of the nerve-endings in the intestinal mucous membrane, with a consequently reflexly excited peristalsis, were not sufficient in number or thoroughness to establish the correctness of the theory.

thirty minims (1.2–2 C.c.) ; SYRUPUS RHEI, ten per cent.,—dose, for an infant, a fluidrachm (4 C.c.) ; SYRUPUS RHEI AROMATICUS,—dose, for an infant, a fluidrachm (4 C.c.) ; TINCTURA RHEI, fifteen per cent., —dose, one to two fluidrachms (4–7 C.c.); TINCTURA RHEI AROMATICA, twenty per cent.,—dose, one-half to one fluidrachm (2–4 C.c.) ; TINCTURA RHEI DULCIS, ten per cent.,—dose, two to three fluidrachms (7–11 C.c.). The aromatic preparations are of pleasant taste and efficient, and are much used for children.

ALOE—ALOES. U.S.

There are three commercial varieties of aloes, which are all obtained in a similar manner,—*i.e.*, by cutting off the thick, succulent leaves of the various plants, standing them up, allowing the juice to drain into suitable vessels, and afterwards inspissating, either by exposure to the sun or by slowly evaporating. The leaves contain a very large amount of a thick, mucilaginous juice, which escapes on pressure ; hence aloes prepared by expressing the leaves or by boiling them—both of which processes are sometimes practised—is very inferior. *Socotrine Aloes* is the product of Aloe Perryi, which grows in the island of Socotra in the Indian Ocean, and on the southern coast of Arabia. *Barbadoes Aloes* is prepared in Barbadoes and other West Indian islands, from Aloe vera. These two varieties are recognized by the U. S. Pharmacopœia. *Cape Aloes* is obtained in the Cape Colony, South Africa, from Aloe spicata.

Aloes are darkish extracts, of a bitter, nauseous taste, yielding their virtues to alcohol, imperfectly to water, and very perfectly to alkaline solutions. Of these varieties the Socotrine is most esteemed in human medicine. The Barbadoes is said to be the strongest, but is employed almost exclusively in veterinary surgery.

T. and H. Smith[33] in 1850 discovered in Barbadoes aloes a crystalline principle,—aloin,—which was shortly afterwards found by Pereira to exist already crystallized in the sap of various species of aloe-plants, and was subsequently obtained by Groves[34] from Socotrine aloes. *Aloin* crystallizes from its watery solution in sulphur-yellow granules, from a hot alcoholic solution in star-like groups of needles. It is neutral, odorless, of a taste at first sweetish, afterwards intensely bitter ; is soluble with difficulty in cold water, freely in boiling water and in alcohol. There are three varieties of aloin,—*barbaloin*, *socaloin*, and *nataloin*, obtained respectively from the Barbadoes, the Socotrine, and the Cape aloes. *Aloinum*, U. S., is the aloin derived from Barbadoes aloes or from Socotra or Zanzibar aloes. The aloin of commerce is chiefly barbaloin, and is certainly an active cathartic in doses of half a grain to a grain.

H. Meyer[35] finds that the Barbadoes and Curaçoa aloin act both on man and on many lower animals as a purgative, whilst the Natal aloin fails ordinarily to affect man, although it is a certain cathartic in dogs and cats. The time required for the Barbadoes aloin to produce purgation was from eight to thirty hours, which Meyer believes to be due to the fact that its physiological action depends upon its

undergoing chemical change in the intestines. In order to facilitate this change he exhibited with it potassium carbonate and ferrous sulphate, and found that these salts markedly hastened the effect. He also found that Natal aloin, when given to persons who had been fed for six days an exclusively animal diet, acted as a cathartic.* In the lower animals Kohn[36] found the hypodermic injections of aloin to cause gastro-enteritis with albuminous urine, and a peculiar inflammation of the kidneys; 0.1 gramme of Merck's aloin for every kilogramme of bodily weight was a fatal dose for the dog. Aloin could be detected in the urine. (Method of analysis given.) Brandenburg[37] has experimentally shown that very large doses of aloin cause in the rabbit a fatal necrosis of the renal epithelium; small doses produce a parenchymatous nephritis.

PHYSIOLOGICAL ACTION.—Aloes is a stomachic, stimulant cathartic, remarkable for the slowness of its action. It has been supposed to influence chiefly, if not solely, the large intestine, and the clinical evidence is very strong that in overdoses it produces irritation of the rectum. The belief, formerly universal, that it is capable of producing hemorrhoids, and the statements that its habitual use in large doses causes tenesmus, a feeling of weight, heat, and uneasiness in the pelvis, and occasionally excitation of the sexual organs, are of very doubtful correctness. Aloin has been detected in the urine by J. Dietrich[38] and also by Meyer.

THERAPEUTICS.—Aloes, being a stimulating purgative, is chiefly used in the *constipation* of atonic subjects. In the constipation of plethora it should not be employed; neither should it be administered when active abdominal or rectal inflammation exists. During pregnancy it is best avoided, and large purgative doses should never be given. Formerly it was taught that aloes should not be used in *hemorrhoids;* but most, if not all, of the cases of this affection depend upon a condition of relaxation of the rectal veins, and Fordyce Barker[39] insists upon the great value of aloes in piles, and states that Oppolzer was especially famous for his treatment of this affection, and that his prescriptions were, when piles are associated with constipation, aloes and quinine; without constipation, aloes and sulphate of iron. For bleeding piles he used ℞—Ferri sulphat., ℈i; Ext. aloës aq., ʒi; Ext. taraxaci, q. s. Ft. pil. no. 60. S.—One morning and evening, and increase to three a day if necessary. When costiveness accompanies atonic *amenorrhœa*, aloes alone of all the laxatives should be exhibited; and it is also of service in atonic *menorrhagia*.

ADMINISTRATION.—As aloes often contains sticks and other extraneous matters, the U. S. Pharmacopœia directs that an ALOE PURIFICATA, or *Purified Aloes*, should be made by dissolving the crude drug in alcohol, straining, and evaporating. Of this the full purgative dose is ten to twenty grains (0.6–1.2 Gm.). The official preparations of crude aloes have been almost entirely superseded by aloin.

* Consult *Chem. Gaz.*, 1851; *Die Pflanzenstoffe*, 1047; *Trans. Brit. Pharm. Soc.*, 1872; *Brit. Med. Journ.*, 1887, i. 747; *Bull. Thérap.*, xci. 259; *Lond. Med. Record*, 1877, 459; and *Edin. Med. Journ.*, xx. 1002.

The tincture (TINCTURA ALOES—ten per cent., U. S.),—dose, as a laxative, one to three teaspoonfuls; the tincture of aloes and myrrh, ELIXIR PROPRIETATIS (TINCTURA ALOES ET MYRRHÆ—aloes and myrrh, of each ten per cent., U. S.),—dose, as a laxative, one to two teaspoonfuls; the pills (PILULÆ ALOES, U. S.), which contain each two grains of aloes and two grains of soap; the *Pills of Aloes and Asafetida* (PILULÆ ALOES ET ASAFŒTIDÆ, U. S.), useful in *costiveness* of hysterical or old subjects, each pill containing four grains of a mass composed of equal proportions of aloes, asafetida, and soap; the *Pills of Aloes and Mastich* (PILULÆ ALOES ET MASTICHES, U. S.), the famous *Lady Webster Dinner-Pill*, each containing two grains of aloes; the *Pills of Aloes and Myrrh* (PILULÆ ALOES ET MYRRHÆ, U. S.), used in *amenorrhœa*, and containing two grains of each ingredient in every pill; the *Pills of Aloes and Iron* (PILULÆ ALOES ET FERRI, U. S.), containing each one grain of aloes and one of dried ferrous sulphate.

Aloin is actively purgative in dose of half a grain (0.03 Gm.); laxative dose, one-fourth of a grain (0.016 Gm.). Under the name of *A. B. S. Pill*, a combination of Aloin, gr. $\frac{1}{6}$; Extr. belladonna, gr. $\frac{1}{12}$; Strychnine sulphate, gr. $\frac{1}{120}$, is very largely used as a laxative.

SENNA—SENNA. U. S.

Under the name of Senna various species of the genus Cassia have found their way into commerce, but at present the U. S. Pharmacopœia recognizes only the leaflets of the Cassia acutifolia of Nubia and Upper Egypt (*Alexandria Senna*), and of the Cassia angustifolia of Southern India (*Tinnevelly Senna*). The senna-leaves vary from three-fourths of an inch to an inch and a half in length, and are to be distinguished by the inequality of their bases, the two sides of the lamina or leaf-blade joining the midrib at unequal heights and angles. *Alexandria Senna* is characterized by the presence of the shorter *argel-leaves*, with equal bases, by the ovate-pointed leaflets of Cassia acutifolia, and by the scattered mucronate-obovate leaflets of C. obovata. *India Senna* is distinguished by the oblong leaflets, from one to two inches in length, entire and perfect. Owing probably to the fact that it is largely cultivated in the southern portion of the peninsula of Hindostan, especially near Tinnevelly, this senna at present constitutes the greater part of that which is sold in the drug-stores. *Cathartic Acid*, discovered by Dragendorff and Kubly,[40] is its chief active principle. According to Groves, four grains of the *ammonium cathartate* will purge actively, whilst R. Stockman[41] has shown that rabbits may be purged to death by a cathartate given by the mouth, although these salts have no effect upon the animal when injected into the blood or given subcutaneously.

THERAPEUTICS.—Senna is a very powerful, somewhat irritating hydragogue cathartic, acting, it is said, as readily upon swine, dogs, cats, and horses as upon man. When given alone, it is very apt to gripe severely, and is consequently more often used in combination. In obstinate *fecal accumulation* the Black Draught constitutes a most efficient and safe remedy.

In small doses it is often used as a laxative. Its infusion injected into

the veins is said to cause both vomiting and purging, and the milk of nursing women taking it is affirmed to act as a cathartic. An aromatic should be administered with senna, to lessen its tendency to gripe. The leaves are not given in substance. The dose of the fluid extract (EXTRACTUM SENNÆ FLUIDUM, U. S.) is two fluidrachms to half a fluidounce (8–15 C.c.); the confection (CONFECTIO SENNÆ, U. S.) is a very complex but elegant preparation, used only as a laxative, in doses of one to two drachms (4–7 C.c.), especially in *pregnancy;* it is not suited to dyspeptic cases, on account of its tendency to derange the digestion. INFUSUM SENNÆ COMPOSITUM, six per cent., U. S. (*Black Draught*), contains manna and magnesium sulphate,—an efficient hydragogue purge, causing very large watery discharges when given in dose of four fluidounces (120 C.c.); the dose of the syrup (SYRUPUS SENNÆ—twenty-five per cent., U. S.) is one to four fluidrachms (4–15 C.c.); the PULVIS GLYCYRRHIZÆ COMPOSITUS, U. S., or *Compound Liquorice Powder*, is an excellent, pleasant laxative in doses of thirty to sixty grains (2–4 Gm.).

SALINES.

MAGNESII SULPHAS. U. S.—*Magnesium Sulphate.—Epsom Salt* ordinarily occurs in small, acicular, slowly efflorescent crystals, containing about fifty-one per cent. of water of crystallization, soluble in their own weight of water at ordinary temperatures. The taste is bitter, saline, and nauseous.

PHYSIOLOGICAL ACTION.—Epsom salt is a most active hydragogue cathartic, producing very large watery discharges without causing any irritation of the intestines. The soluble magnesium salts injected into the blood are powerful poisons, causing death by failure of respiration, and also depressing the heart (J. H. Recke,[43] also M. Hay). These effects, are, however, never perceptible in the ordinary use of the magnesium sulphate, but recorded cases show that the drug is capable of acting as a violent general poison. Christison reports a boy, ten years old, killed by two ounces, without the induction of purgation. W. Sang[44] reports as caused by four ounces of Epsom salt in a very concentrated solution, burning pain in the stomach and bowels, great dyspnœa, and collapse, with dilated pupils, muscular relaxation, and finally coma, ending in death, without purging or vomiting. In J. H. Neale's case the symptoms were violent enteritis, with most alarming heart depression, from which, however, the patient recovered. In the researches of Curci,[45] it was found that the soluble magnesium salts first increase the blood-pressure and slow the pulse, and then lower the blood-pressure and quicken the pulse, causing finally cardiac paralysis. As the rise of the arterial pressure is prevented by previous destruction of the vaso-motor centres, it is probably the result of centric stimulation.*

* The action of the saline purgatives upon the tissue-changes of the body has been laboriously investigated by a large number of chemists, with results which are so dis-

Epsom salt is very largely used when it is desired to deplete or to promote absorption through the bowels, as in *dropsies;* or to relieve congestion of the bowels themselves, as in *enteritis* or *colitis;* or when it is necessary to soften down *fecal accumulation,* as in obstinate constipation. The dose is half an ounce to an ounce (15–30 Gm.), properly diluted. M. Luton[45] affirms that ten centigrammes (1.53 gr.) administered hypodermically usually provoke several watery stools; but the practice seems to us a very doubtful one.

Liquor Magnesii Citratis. U. S.—*Solution of Magnesium Citrate* is prepared by putting into a strong bottle a syrupy solution of magnesium citrate containing an excess of citric acid, adding potassium bicarbonate, and corking tightly. On account of its agreeable taste and effervescence, this preparation is much used as a purgative. It is similar to Epsom salt in its action, but is less efficient, more apt to gripe, and more irritating. It ought not to be used in inflammatory affections of the bowels.

Magnesii Citras Effervescens. U. S.—*Effervescent Magnesium Citrate* contains less free acid than the solution, and is therefore somewhat less pleasant to the taste. The dose is one to three teaspoonfuls taken in solution while effervescing.

Sodii Sulphas. U. S.—*Sodium Sulphate,* or *Glauber's Salt,* occurs in six-sided, very efflorescent, striated prisms, which finally crumble into a white powder. It acts like Epsom salt, but is more powerful; it is, however, little used on account of its extremely nauseous taste. It is the chief active principle of many natural purgative waters which are so useful in chronic gastric and other abdominal catarrhs with constipation. The combination of two ounces of sodium phosphate, one-half ounce of sodium sulphate, and one-half drachm of potassium iodide, taken in full laxative doses, well diluted, upon rising, is often very efficient in such cases as are benefited by Carlsbad waters. Dose of sodium sulphate, one-quarter to one-half ounce (8–15 Gm.).

Sodii Phosphas. U. S.—*Sodium Phosphate* occurs in colorless, transparent crystals, which effloresce and become opaque on exposure. It is a tribasic phosphate, one part of water acting as a base. It is soluble in 5.8 parts of cold water, and has a saline taste, closely resembling that

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cordant that it does not seem at present possible to come to any conclusion. The drift of the evidence, however, seems to us to show that the direct action upon tissue-change is very slight, and that it is incapable of producing a definite and fixed result amidst the varying and complicated daily causes which inevitably produce more or less disturbance and variation in the nitrogenous elimination. An elaborate research upon the subject has been published by London in the *Zeitschr. f. Klin. Med.*, xiii. 1. Most of the literature of the subject will be found in this article, the original work of which seems to lead to the conclusion just stated.

of common salt. In large doses it is a mild saline purgative, but as such is not at present very much employed. Sodium phosphate is a very useful remedy in chronic *infantile diarrhœa* with intestinal indigestion, especially as it occurs in bottle-fed subjects. It appears to have a specific action upon the liver and also upon the intestinal glands in general, so that it is often of great service where there are habitually chalky stools or white fluid motions, and in many cases of green stools. In *chronic hepatic torpor* and in *catarrhal jaundice* it is often used with great advantage, and it seems sometimes of value in *lithæmia*. In his thesis of 1888 Haig affirmed, as the result of his experiments, that sodium phosphate has very pronounced effect in increasing the excretions of uric acid. In a subsequent paper, however, he stated that if the phosphate contain any sulphate, or if it be in the form of the acid phosphate, or meet with an acid in the stomach which should make it an acid phosphate, it has no power in increasing uric acid excretion ; so that it seems to us that at present we cannot consider sodium phosphate as having distinct relations with uric acid excretion. Dose for children, from ten grains (0.6 Gm.) upward ; for adults, from twenty to forty grains (1.2–2.6 Gm.); as a laxative, half an ounce (15 Gm.).

Potassii et Sodii Tartras. U. S.—*Potassium and Sodium Tartrate*, or *Rochelle Salt*, is made by the addition of sodium carbonate to a solution of potassium bitartrate. It occurs in large, colorless, transparent, slightly efflorescent, prismatic or half-prismatic crystals, which are soluble in two and a half parts of cold water, and have a slightly saline taste. It is a mild saline purgative, decidedly less efficient, but much less offensive to the palate, than Epsom salt. The dose is from half an ounce to two ounces (15–60 Gm.), properly diluted.

Pulvis Effervescens Compositus. U. S.—*Seidlitz Powder* is in two packets ; the white paper contains about thirty-five grains of tartaric acid, the blue paper forty grains of sodium bicarbonate and two drachms of Rochelle salt. When they are taken, the powders are dissolved separately, the solutions added, and the whole drunk while effervescing. They are very acceptable to the stomach, refrigerant and laxative rather than purgative. Seidlitz powders are used almost exclusively to evacuate the bowels, and exhibited after blue mass to " carry off " mercurials, etc. They should be taken on an empty stomach, as before breakfast. One powder is the usual dose ; but not rarely even two powders will fail to purge.

DRASTICS.

As already stated, the *drastics* are those vegetable cathartics which are actively irritant. With perhaps one or two exceptions, in sufficient amount they are capable of causing fatal gastro-intestinal irritation. The line between the drastics and the stronger purgatives is, of course,

placed more or less arbitrarily, since the various cathartics differ in action almost by insensible degrees. Thus, jalap, although included among the drastics in this work, might with perhaps even greater propriety be classed among the purgatives, since it is very little more active or irritant than is senna. Further, these remedies in combination seem to lose, in a measure, their power of causing irritation, and to become useful purgatives. A fact, however, which makes the classification here employed clinically useful, although it be not scientifically accurate, is that none of these remedies should be used when a purgative is desired to relieve gastro-intestinal inflammation or irritation ; and, on the other hand, when a revulsive action is wished for, as in some cases of brain disease, one of the drastics should always be selected.

JALAPA—JALAP. U.S.

The tuber of Ipomœa Jalapa, a convolvulaceous vine growing in Mexico. Jalap comes into the market in two forms : one, that of the younger roots, which are sold undivided ; the other, that of the old roots, which are brought into the market in transverse or longitudinal slices and in pieces. The first variety consists of very hard, irregularly globular, brittle roots, about the size of a shut fist, or smaller, and often slashed with vertical incisions, made for the purpose of facilitating drying. The active principle of jalap is a resin, variously known as *rhodeoretin* or *convolvulin*, closely allied to the resin of scammony.

PHYSIOLOGICAL ACTION.—Upon dogs and horses jalap (Stillé[46]) is said to act as a powerful hydragogue cathartic, and in overdoses as a gastro-intestinal irritant. Its active principles are absorbed, since Cadet de Gassicourt produced diarrhœa in dogs by the free application of jalap to the shaven skin, and J. Müller[47] found the resin in the blood of dogs to which he had given it. Stillé, however, asserts that it does not impart its purgative properties to the milk of nursing women, and that in man it is not absorbed by the skin. In man jalap produces free hydragogue catharsis, often with nausea ; or, if in overdoses, violent vomiting and purging.

THERAPEUTICS.—Jalap is especially indicated when it is desirable to produce large watery stools. It is, however, very rarely used alone. A favorite combination with many practitioners is of it and calomel. In the form of the compound powder (PULVIS JALAPÆ COMPOSITUS, U. S., —jalap, thirty-five parts, cream of tartar, sixty-five parts), jalap is very frequently used with great advantage in *ascites* and also in other forms of general *dropsy*. It is believed when given in this way to exert some influence upon the renal functions : for very many cases the proportion of cream of tartar in the official compound powder is too small.

ADMINISTRATION.—The dose of powdered jalap is ten to twenty-five grains (0.6–1.6 Gm.), of the extract (EXTRACTUM JALAPÆ, U. S.), ten to twenty grains (0.6–1.3 Gm.). The resin (RESINA JALAPÆ, U. S.),

like the other purgative resins, is tasteless. Dose for adult, from two to four grains (0.13–0.26 Gm.).

COLOCYNTHIS—COLOCYNTH. U.S.

The fruit, deprived of its rind, of Citrullus Colocynthis, or bitter cucumber, a vine growing in South Africa, Japan, Syria, Egypt, Turkey, the islands of the Grecian Archipelago, etc. The fruit is a round gourd, from two to four inches in diameter, of a whitish or pale yellow color. It occurs in the market with or without its rind. The pulp is dry and membranous, whitish, and contains the active purgative glucoside *colocynthin*, first discovered by Herberger.

Colocynth in large dose is an irritant hydragogue cathartic, entirely capable of destroying life, and, according to Orfila and Schroff, acting upon the lower animals as upon man. Christison records the death of a woman twenty-four hours after taking a teaspoonful and a half of the powder. Roques chronicles a fatal result produced by less than a drachm of the powder in decoction, but, on the other hand, narrates a case in which three drachms failed to kill (Husemann[48]), and W. A. Rolfe reports recovery after a quarter of an ounce of the powdered drug. Pregnancy existed, but abortion was not produced.

ADMINISTRATION.—It should not be used in *dropsy*, and is employed almost solely in combination with other purgatives. The full purgative dose of the extract (EXTRACTUM COLOCYNTHIDIS) is three to five grains (0.2–0.3 Gm.), and of the compound extract (EXTRACTUM COLOCYNTHIDIS COMPOSITUM, U. S.), which contains extract of colocynth, sixteen parts, purified aloes, fifty parts, resin of scammony, fourteen parts, cardamom, six parts, soap, fourteen parts, as a laxative, one to three grains (0.06–0.2 Gm.); as an active purgative, five to twenty grains (0.3–1.3 Gm.).

SCAMMONIUM—SCAMMONY. U.S.

A resinous exudation from the root of Convolvulus Scammonia, a vine growing in Syria. It is said to be obtained by cutting off the root obliquely about two inches from the origin of the stems, and catching in shells the few drachms of milky juice which exude from each root. From these shells it is emptied into a vessel and allowed to concrete. Formerly scammonium was adulterated to a great extent with chalk, flour, ashes, sand, etc., constituting the *Factitious Scammony* of authors. *Scammonin*, the active resin of scammony, is believed to be identical with *jalapin*, originally separated by Mayer from male jalap, and closely allied to *convolvulin* of true jalap. The Pharmacopœia requires that scammony shall contain seventy-five per cent. of this resin. Therapeutically scammony acts like jalap, but is somewhat more irritating. It is almost solely used in combination with other cathartics, and on account of its frequent adulteration should be given in the form of the resin (RESINA SCAMMONII, U. S.). Dose, from two to five grains

(0.13–0.3 Gm.). The pure or *Virgin Scammony* is in irregular, rough, fissured masses, of various sizes, commonly solid, with a dull resinous fracture, and of a dark greenish color, inclining to black. The smell resembles that of old cheese.

PILULÆ CATHARTICÆ COMPOSITÆ. U. S.—*Compound Cathartic Pills* contain each, approximately,—compound extract of colocynth, one and a third grains; extract of jalap and calomel, each one grain; gamboge, one-fourth of a grain. As there is soap in the first ingredient, the calomel is sooner or later reduced to the black oxide of mercury.

The compound cathartic pills are very efficient purgatives, generally not producing much griping. They cause large watery stools, and are used when it is desired to empty the bowels and deplete from the portal circulation. On account of the mercury which they contain, as an habitual laxative they are much inferior to the vegetable cathartic pill (PILULÆ CATHARTICÆ VEGETABILES, U. S.), one or two of which will usually act kindly and efficiently.

PODOPHYLLUM—PODOPHYLLUM. U.S.

The rhizome of Podophyllum peltatum, or May-apple, a perennial herb, growing in the Northern and Middle United States. Podophyllum occurs in simple or branched, cylindrical, brownish pieces, about the thickness of a goose-quill, smooth or wrinkled longitudinally, often obscurely marked with the scars of leaf-scales, and furnished with numerous rootlets or their remnants attached to the lower surface. The taste is bitterish, acrid, and nauseous. The rhizome contains the alkaloid *berberine*, but the purgative power resides chiefly in *podophyllotoxin** of Podwyssotzki,[49] although it is probable that there are other purgative substances in the rhizome, especially an uncrystallizable resin, *podophylloresin*.

Podophyllum is a rather slowly acting, but very thorough cathartic, whose large dose either in man or in most of the domestic animals produces violent purging, with great pain, and often with vomiting; the symptoms increasing, if the dose have been sufficient, to excessive hypercatharsis, with bloody stools, great prostration, and death. It is said to act when given hypodermically.† A child four years old was killed by an unknown amount. The symptoms were repeated vomiting, slight purging, collapse, and finally coma, ending in epileptiform convulsions (T. G. Morton). An infant twenty-two months old recovered from four grains.[50]

* Podophyllotoxin was believed by its discoverer to be composed of *picropodophyllin* in combination with *podophyllinic acid*. The latest chemical researches indicate, however, that these substances are decomposition products. Podophyllotoxin appears to be a very irritant, active cathartic, and has been used in medicine in doses of one-fifteenth of a grain. According to J. Neuberger (*Arch. f. Exper. Path. u. Pharm.*, 1890, xxviii.), it causes in the lower animals violent purging and severe nephritis, with fall of the arterial pressure and death from exhaustion.

† See *Amer. Med. Times*, iv.; also *Med. Times and Gaz.*, March, 1863.

In therapeutic doses it is believed by very many practitioners to act especially upon the liver, and is much used in acute *constipation* and in so-called *bilious attacks*. As ten or more hours are usually required for its action, it should not be combined with quick cathartics. With calomel it acts very well. The only preparation that should be used is the resin (RESINA PODOPHYLLI, U. S.), or *podophyllin*, the laxative dose of which is one-twelfth to one-sixth grain (0.005–0.01 Gm.), the purgative dose, one-sixth to one-half grain (0.01–0.03 Gm.). It is very advantageously combined with extract of belladonna.

ELATERIUM.

A substance deposited by the juice of the fruit of Ecballium elaterium, or squirting cucumber, a native of Greece, but cultivated in England. In the interior of the ovate fruit is an elastic sac, which contains the seeds, and at ripening becomes so distended with juice that when the fruit falls off the vine, and the support is removed from the stem end, a rupture occurs at the latter position, and the liquid with the seeds is forcibly projected. The medicinal principle is said to be contained only in this inner juice. In order to avoid loss, the fruit is picked with a piece of the stalk adherent to it before ripening, and is opened by slicing. *Elaterium* occurs in light, friable, slightly incurved, greenish-gray cakes about a line thick. The taste is acrid and bitter, the fracture finely granular. Owing to the variability of commercial elaterium, the U. S. Pharmacopœia now recognizes only the active principle, *Elaterin* (ELATERINUM, U. S.), which was first separated in a pure state by Morries.[51] It crystallizes in colorless, shining, rhombic, six-sided, odorless tables, of a very bitter sharp taste and neutral reaction.

PHYSIOLOGICAL ACTION.—Locally applied, elaterium is a very decided irritant, producing, according to Pereira, ulcerations in the fingers of those who handle the fruit and prepare the drug for market. When taken internally, it acts on man as a most powerful hydragogue cathartic.

On the lower animals its action is much less certain. Viborg asserts that a horse was unaffected by a pound of elaterium fruit; and H. C. Wood has given one and even two grains of a presumably active elaterium to a dog without producing very obvious results. If the dose be sufficiently large, all animals probably are, however, fatally affected by elaterium, perishing by progressive depression. Stillé[52] asserts that the death is not rarely preceded by violent vomiting and purging; and even when these are absent during life, post-mortem examination reveals congestion and inflammation of the gastric and intestinal mucous membranes. In none of our own experiments, which have not been numerous, has any purging been present; further, in Köhler's[53] elaborate investigation, elaterium dissolved in alcohol was injected under the skin, the powdered elaterium was put into the rectum, and was given by the mouth after the gall-duct had been tied so as to prevent the flow of bile into the intestine, and in neither case was there any purging, but prostration, apathy, disturbed respiration, salivation, and violent convulsions, ending in death. From these experiments Köhler draws the conclusion that elaterium exerts a general action upon the system, for which its introduction into the blood is all that is requisite, and also a purgative influence, for which it is necessary that there be bile in

the duodenum to dissolve the elaterium and cause it to act locally on the intestine. The objection to this conclusion is that it seems probable that elaterium does not purge dogs and rabbits, even when given by the mouth. Further, elaterium applied externally will cause purging in man (Stillé). So that the application to man of the conclusions arrived at by Köhler is incorrect. Köhler's experiments proved that in animals elaterium is absorbed, even when given by the mouth, since he found it in the urine of poisoned dogs and rabbits.

THERAPEUTICS.—Elaterium is certainly the most efficient of all the hydragogue cathartics, producing in properly regulated doses the freest evacuations with comparatively little pain and irritation. It is the most efficient of all the medicines of the class in general *dropsy* or in *ascites*. As, however, its action is very exhausting, great care should be exercised not to give it in too large doses, and also to support the strength of the patient during the period of purgation, and afterwards, by alcoholic stimulants, easily digested nutritious food, and appropriate hygienic measures. In the latter stages of dropsy the injudicious use of elaterium may cause a fatal exhaustion. For the asserted power of elaterium in increasing the intestinal elimination of urea we have been unable to find authority. Clinical experience has, however, demonstrated the value of elaterium in *uræmia*. In order to deplete, elaterium has been employed in various diseases; but this use is not to be encouraged, and especially when there is any gastro-intestinal irritation or inflammation are the salines much preferable to elaterium.

Elaterium is without doubt capable of destroying life, but we know of but one recorded death,—that of a woman in whom two and two-fifths grains of the extract of elaterium and sixteen grains of rhubarb caused uncontrollable vomiting and purging, ending in a fatal gastro-enteritis.*

Dose, one-sixth of a grain (0.01 Gm.), combined with extract of hyoscyamus or of belladonna and an aromatic oil. Dose of the official elaterin, one-twentieth of a grain (0.003 Gm.); of the trituration (TRITURATIO ELATERINI—ten per cent., U. S.), half a grain (0.03 Gm.). Elaterium when injected hypodermically purges freely, but also produces an excessively severe local irritation, even fatal tetanus.†

CAMBOGIA—GAMBOGE. U.S.

A gum resin, obtained in Siam by breaking off the leaves and young shoots of the tree known by botanists as Garcinia hanburii and catching in suitable vessels the juice as it drops. When the receptacles consist of hollow bamboos, the juice hardens into cylindrical casts, striated externally, and with a central cavity due to the loss of substance in drying. This is the so-called *pipe gamboge*. *Gamboge in sorts* occurs in irregular masses. Gamboge is a hard, resinoid substance, of a brittle, often conchoidal fracture, of a deep reddish-orange color on exposed surfaces, more yellowish when freshly broken, affording a bright yellow powder,

* See *Beck's Medical Jurisprudence*, 12th ed., ii. 719.
† See *Therap. Gaz.*, ii. 27.

insoluble in water, with which it forms, however, an intensely yellow emulsion. It has little or no taste, but when chewed produces, after a time, an acrid sensation in the fauces.

PHYSIOLOGICAL ACTION.—Gamboge acts upon man as a violently irritant cathartic. On the lower animals it has a similar influence, but Schaur and Orfila state that when in large dose it often fails to purge, producing rapidly fatal gastro-enteritis, so intense as seemingly to paralyze the bowels. According to Daraszkiewicz [54] and to Schaur, in order for gambogic acid to act as a purgative the presence of bile in the intestine is necessary. Schaur and Richter affirm that gamboge upon raw surfaces acts simply as an irritant: further, Gmelin and Tiedemann assert that they have found its principles in the urine; it may therefore well be that solution by the alkaline fluids of the intestines is necessary for its purgative action. Lewis, Abeille, and Ferriar state that, when given in certain ways, gamboge acts as a decided diuretic. If this be true, absorption of its active principle must occur. Schaur was not able, however, to detect it in the urine of persons or of animals taking it. Even when he injected large quantities of it into the blood of dogs he failed to find it in the urine, although he did obtain a resinoid substance which he believes to be a derivative.

Gamboge is so irritant that it is used in practical medicine only to give sharpness to purgative combinations. The full purgative dose would be from two to five grains (0.13–0.3 Gm.).

OLEUM TIGLII—CROTON OIL. U.S.

The fixed oil obtained from the seeds of Croton Tiglium, a euphorbiaceous shrub of Hindostan and other portions of Southern Asia. This oil is quite viscid, varies in color from a pale yellow to a dark reddish brown, and has an acid reaction. Its taste is hot, acrid, and extremely persistent; its odor faint, but peculiar. Croton oil consists chiefly of the glycerites of ordinary fatty acids, but contains also *crotonoleic acid*, which has been supposed to be its pure active principle, but is stated by Dunstan and Boole to be a mixture of inactive oily acids with a powerfully vesicating, resinous substance, *croton-resin*.

THERAPEUTICS.—Locally applied, croton oil is an intense irritant, producing upon the skin an eruption which is at first papular but in a very short time becomes pustular.* (See COUNTER-IRRITANTS.) Administered internally, croton oil produces in man and in most of the lower animals violent purging, with severe griping, and is capable of causing a fatal gastro-enteritis. Its action on the intestine is probably in part local and in part through absorption. In the experiments of Hertwig (quoted by Stillé) and of Buchheim,[55] purgation did not follow the injection of the oil into the veins of animals; but Conwell obtained a result contrary to this, and there is considerable testimony that its external use in man is

* For a histological study of the eruption, see *Wiener Med. Wochenschr.*, 1897, xlvii. 1021.

sometimes followed by purging (Stillé), and even by fatal results.* The experiments of Kobert and of Hirschheydt[56] seem to prove that crotonoleic acid is both the purgative and vesicant active principle: it exists in the oil combined with glycerin. It is believed that the glycerite is slowly decomposed in the intestines, and that the acid which is thus set free acts progressively. Certainly, Hirschheydt found that pure crotonoleic acid, which has appeared in commerce, is not a practical purgative, ten milligrammes being very uncertain in their effects, whilst large doses are prone to produce excessive gastro-intestinal irritation. Injected into the blood, crotonoleic acid was found to be an exceedingly active depressant to the circulation. The amount of free crotonoleic acid in croton oil increases very markedly with age. On this account old croton oil, with an acid reaction, acts much more harshly than does the recent neutral or nearly neutral oil, and should be rejected for internal use.

Croton oil is chiefly used in practical medicine in *mania*, *apoplexy*, or other diseases in which there is difficulty in administering a cathartic. It is also given in cases of very obstinate constipation when less active remedies have failed. It is the one cathartic employed when, as in some brain diseases, it is desired to revulse by the intestines. The dose is one drop, in emulsion, or by simply placing it upon the tongue. In overdoses, croton oil is a violent poison.

Toxicology.—Although in small amounts croton oil causes such severe symptoms, yet in larger quantities it has failed to produce as serious results as would be naturally expected. It is, however, very possible that in at least some of the recorded cases the oil was adulterated. Cowan has reported a case (Husemann[57]) of a child four years old who recovered in two days from a teaspoonful of croton oil taken on a full stomach; Adams (Husemann) saw recovery in an adult after the ingestion of a drachm; and the case is recorded of a woman[58] who took about an ounce, was vomited forty-five minutes afterwards with mustard, and finally recovered. The minimum fatal dose is not known, and probably varies greatly. A child[59] aged thirteen months was killed by a quantity believed not to exceed three minims. Giacomini (Stillé) reports a case in which twenty-four grains of the drug proved fatal in as many hours: although there were but four stools, the patient presented the symptoms of general collapse, preserving consciousness to the last. A little less than two drachms has caused vomiting and death without purging.[60] †

The treatment of croton-oil poisoning is purely symptomatic. Opium should be given to lessen the purging, demulcent drinks to lessen the irritation. If collapse develops, cardiac stimulants should be administered hypodermically and bodily temperature maintained by the application of external heat.

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* See *Schmidt's Jahrb.*, clxiv.; also *Kobert's Arbeiten*, 1890, iv. 45.

† For other cases, see *Med. Gaz.*, xliii.; *Edinb. Med. Journ.*, 1861; *Lancet*, 1870, i.; *Brit. Med. Journ.*, 1874, i.; *Ann. d'Hyg.*, 1871, i.; also *Kobert's Arbeiten*, 1890, iv.

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FAMILY IV.—DIURETICS.

DIURETICS are medicines used for the purpose of increasing the flow of urine. Some of them act directly upon the secreting structure, but others only in some indirect way, as by increasing the blood supply to the kidney. It is notorious that diuretics often fail in practice when their action is most urgently needed. This result arises, in many cases, from the nature of the disease, and is not because diuretics are powerless or uncertain. Thus, in cardiac disease the congestion of the kidneys may be so great as to render secretion impossible; and it is equally evident that when the secretory cells have been destroyed, as in advanced Bright's disease, diuretics must be powerless.

There are certain agencies whose influence upon the kidneys should never be lost sight of in exhibiting diuretics. Thus, cold, by checking the secretion of the skin, often acts as a most efficient remedy of the class. Again, mere vascular fulness tends to provoke excretion of water by the kidneys. E. Roux[1] found that the ingestion of large quantities of water greatly increased the flow of urine, but did not sensibly affect the elimination of urea or uric acid, although the elimination of the chlorides seemed to be augmented; in Böcker's[2] experiments, however, large draughts of water increased not only the amount but also the solids of the urine. The investigations of J. Meyer[3] explain these discrepancies and show how water may be of service in various diseases. Meyer found that when the tissues were full of the products of disintegration, the effect of water in increasing elimination was very marked, but that upon the wasting processes of the body the water exerted no influence. It would seem, therefore, that while we cannot by water produce tissue-disintegration, we can by it wash out the retained products of tissue-change; and the great rarity of uninherited gout in America probably has some connection with the universal habit of drinking water very freely. Large draughts of simple water at regular intervals often act very favorably in *acute Bright's disease*, greatly increasing the urinary flow and at the same time lessening the irritation of the kidneys. The original assertion of Porak and Bernheim,[4] that in violent irritation of the kidneys, in *suppression of urine*, in grave *acute Bright's disease*, and in similar conditions great good could often be achieved by *hypodermoclysis*, is abundantly confirmed. This procedure consists in the injection deep into the cellular tissue of the buttocks of a thoroughly and very recently

sterilized normal salt solution ;* a half-pint to a pint of the liquid, at a temperature of about 100° F., may be slowly introduced without causing local irritation or giving much pain. A fountain syringe placed about three feet above the patient affords sufficient power to slowly force the liquid through a large hollow needle. In various inflammations or *irritations* of the *genito-urinary* organs, as in *gravel*, whenever it is desired to make the secretion less irritating or less concentrated, the value of water as an adjuvant to medicinal diuretics should always be taken advantage of.

That under various circumstances washing out of the blood, or, as Pierre Delbert[5] calls it, *lavage of the blood*, may be useful is shown by his experiments, in which it was found that the free intravenous injection of saline solution commenced immediately after the hypodermic injection of a fatal dose of strychnine in the dog was able to prevent the development of the strychnine-poisoning, the excess of water in the blood evidently causing elimination to almost keep pace with absorption.

There is a very marked antagonism between the bowels, the skin, and the kidneys, so that great activity in the function of one of these emunctories lessens secretion in the others. When a diuretic action is desired, sweating and purging should be avoided. When a diuretic is exhibited, the patient should be kept cool, walking about, if able, or if it is necessary for him to remain in bed he should be covered lightly. Not rarely, a remedy which when administered cold and the patient kept cool afterwards will act as a diuretic, will when it is given hot and the patient kept warm act as a diaphoretic.

The chief indications for the use of diuretics are as follows :

1. *To maintain the action of the kidneys.* It is hardly necessary here to discuss the necessity of excretion to the system. In various kidney diseases this indication is very urgent ; but as the lessened excretion too often depends upon a profound organic alteration of the renal secreting structure, it is evident that very frequently diuretics must fail when most needed. In the great majority of cases in which diuretics are used to fulfil the present indication, only the mildest of the class should be employed. Whenever there is inflammation of the kidneys, even if it be chronic, irritating diuretics should be avoided. When lessened urinary excretion is purely functional in its origin, diuretics are often most serviceable. In fevers especially is it necessary to maintain the action of the kidneys ; for this purpose water should always be freely given during fever. The alkaline diuretics sometimes may be exhibited ; but the most generally serviceable of all remedies of the class in the febrile state is the sweet spirit of nitre.

2. *To evacuate fluid.* For this purpose hydragogue diuretics are employed in all forms of dropsy.

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* *Normal salt solution* is a 0.7 per cent. solution of common salt in distilled or pure water. For practical purposes it can be made by dissolving a teaspoonful of salt in a pint of water.

3. *To soothe and diminish irritation of the genito-urinary organs.* The value of water in fulfilling this and the next indication has already been pointed out. By lessening the acidity of the urine and rendering soluble the uric acid which is present, the alkalies are equally important in carrying out the present and the following indication.

4. *To alter the urinary secretion so as to prevent the deposition of calculous material.* Notwithstanding it has been otherwise asserted, no practical measure has as yet been devised of dissolving a calculus when once formed. Even to alter the urine so as to prevent further deposition is probably impracticable, except in cases of uric acid or phosphatic diathesis.

Diuretics are very naturally divisible into two sets,—the hydragogue diuretics and the depurant diuretics. These classes, of course, grade more or less into each other, but they are sufficiently distinct for practical purposes. The drugs belonging to the first set simply increase the flow of water from the kidneys, and are therefore used chiefly for the relief of dropsy; those of the second division exert a marked sedative action upon the system, and generally do not increase to any great extent the water of the urine, but modify the secretion in one way or another, and are mostly given to render the urine less irritant or for their sedative and eliminative action in acute disease.

Under the heading of stimulant diuretics are considered certain substances which do not of necessity increase the flow of urine, but whose active principles are eliminated by the kidneys, and by actual contact affect the mucous membrane of the genito-urinary organs.

HYDRAGOGUE DIURETICS.

SCILLA—SQUILL. U.S.

The bulb of Urginea maritima, a liliaceous plant growing in the south of Europe, especially on the shores of the Mediterranean. The bulb varies in size from that of a child's head to that of the fist. It is composed of numerous layers or scales, which separate when it is sliced for drying. As kept in the shops, squill is in horny flakes, of a white or red color, becoming leathery when wet, and having an acrid bitter taste. It yields to water and alcohol and also to vinegar.

The nature of the active principle of squill has not been established. A number of glucosides have been described by chemists, and Merck has put upon the market three substances, *scillin*, *scillipicrin*, and *scillitoxin*.* There is, however, no sufficient proof as to which, if any, of these sub-

* Fronmüller has reported (*Memorabilien*, 1879, xxiv. 250) a series of experiments made, upon persons suffering from various ailments, with the scillin, scillipicrin, and scillitoxin of Merck. He found that scillitoxin in doses of 0.45 grain acted as a rather uncertain diuretic, and frequently caused giddiness, headache, and loss of appetite; scillin seemed to be devoid of diuretic properties; while a gramme of a solution of scillipicrin in water (one part in fifty) administered hypodermically usually caused a great flow of urine, without other evil symptoms than some smarting at the place of injection.

stances represents the crude drug. Scillitin of the older writers and of Merck was a complex body.

PHYSIOLOGICAL ACTION.—In small doses squill acts upon man as a stimulating, slightly irritating, diuretic. In large doses it causes great abdominal pain, violent purging and vomiting, lessened or almost suppressed secretion of bloody albuminous urine, with slow pulse, ending, it may be, in collapse, convulsions, and death.

Upon the lower animals squill acts very much as it does upon man, producing vomiting, violent purging, muscular weakness, dulness, stupor, disturbed respiration, muscular weakness deepening into paralysis, tremors disappearing in convulsions, and finally death in the course of twelve or fifteen hours if the dose have been sufficient. In the experiments of Schroff[6] upon rabbits, scillitin of Merck differed from the alcoholic extract of squill in its effect upon the pulse and upon the pupil, and in the post-mortem appearances produced by it, the pericardial, subpleural, and pulmonary hemorrhages, and the gastric erosion produced by the scillitin, being wanting after death from the extract. C. Lupinski[7] found that scillitoxin is a powerful stimulant to the peripheral vagi in the frog, causing slowing of the pulse, and in certain doses diastolic cardiac arrest, and in the dog slowing of the heart. Large doses cause in the frog tetanic contractions of the heart. He also found that in the dog large doses finally paralyze the peripheral vagi and produce a rapid pulse. The arterial pressure is increased, partly, it is affirmed, by the increased cardiac energy, and partly by a peripherally produced vaso-motor contraction.

It is certain that squill contains some substance which acts similarly to digitalis on the heart, and that this is to be found in the extract. Husemann affirms that the extract has no expectorant properties ; that it is a digitalis-like, cardiac stimulant, and acts as a diuretic solely by affecting the renal circulation. Squill is a stimulant to the kidneys, and in overdoses causes an irritation whose result is lessening of the secretion, scanty bloody urine, or absolute suppression of urine, according to the amount of the poison ingested. Its diuretic action has been noted in animals by Schroff and by Chiarenti (quoted by Stillé), and there can be no doubt as to the power that squill has of increasing the watery portion of the urine. We know of no studies upon its action on the urinary solids. According to Stillé, the external application of squill will produce its characteristic effects on the system.

It is a valuable remedy in *dropsy* when the condition of the system is atonic and when there is no disease of the kidney. It may even be used with advantage in *serous effusion* into the *pleura* or the *pericardium* dependent upon chronic inflammation of the membrane, especially in combination with calomel. A pill of one grain each of squill and digitalis is very efficient in *cardiac dropsy ;* sometimes the addition of calomel is advantageous. The one contra-indication to the use of squill is the existence of Bright's disease or of acute irritation of the kidney.

TOXICOLOGY.—According to Husemann,[8] twenty-four grains of squill have caused death. The treatment of the poisoning consists in the evacuation of the stomach and bowels by ipecacuanha and castor oil, if nature

has not already fulfilled the indication ; the free use of opium ; the exhibition of large quantities of water, for its action on the kidneys ; and the usual measures for the relief of gastro-enteritis, if much tenderness be present. Early in the poisoning care should be exercised in the exhibition of alcoholic stimulants, for fear of increasing the gastric irritation ; during the stage of collapse they may be imperatively demanded, and with their use should be combined that of dry heat applied externally, and of the other usual measures of relief during collapse.

ADMINISTRATION.—As a diuretic, squill should be given in solid form, one or two grains (0.06–0.12 Gm.) every three hours, the dose being gradually increased until some nausea is felt. The preparations of squill are the tincture (TINCTURA SCILLÆ—fifteen per cent., U. S.), —dose, ten to twenty minims (0.6–1.2 C.c.) ; the vinegar (ACETUM SCILLÆ—ten per cent., U. S.),—dose, ten to twenty minims (0.6–1.2 C.c.) ; the syrup (SYRUPUS SCILLÆ, U. S.),—dose, half to one fluidrachm (2–4 C.c.); and the fluid extract (EXTRACTUM SCILLÆ FLUIDUM, U. S.),—dose, one to three minims (0.06–0.18 C.c.).

SCOPARIUS—BROOM. U.S.

Scoparius is the dry tops of Cytisus Scoparius, or the common broom-plant of Europe, which is cultivated in this country and has in some places escaped from the gardens. It occurs as greenish twigs, with minute downy leaves, has a bitter nauseous taste, and, when bruised, a peculiar odor, and yields its virtues to hot water. Stenhouse discovered in scoparius a neutral crystallizable principle, *Scoparin*, which probably represents the purgative and diuretic influences of the drug, and also a liquid alkaloid, *Sparteine*. (See page 328.)

In overdoses, scoparius causes free purging, and even vomiting ; but as ordinarily administered it is an efficient hydragogue diuretic, which is much used in general *dropsy*, and is one of the most reliable remedies of its class. It is best given in decoction,—half an ounce of the tops in a pint of water boiled down to half a pint ; of this an ounce may be given every three hours until some effect is produced ; or a fluid extract, which is not official, may be given in half-drachm doses.

CALOMEL.—Many years ago therapeutic writers, notably George B. Wood, asserted that the combination of digitalis, squill, and calomel yields in the treatment of dropsy, and especially of cardiac dropsy, diuretic results much superior to either of the vegetable products alone ; but more recently E. Jendrassik[9] directed attention to the great practical value of calomel as a diuretic.

The theory that mercury acts by increasing the amount of urea and thus provoking increased diuresis is hardly tenable.* W. Cohnstein[10] has found that the hypodermic injection of mercurial solutions produces

* See Noel Paton (*Brit. Med. Journ.*, 1886, ii.).

a very quick and active diuresis in the rabbit. According to Brasse and Wirth,[11] when mercury is given hypodermically in large dose it soon appears in the urine, which is markedly increased in quantity; if, as not rarely happens, the urine becomes albuminous, excretion of mercury at once ceases, albumin and mercury never coexisting in the urine. Silva,[12] experimenting with defibrinated blood, finds that the addition of a mercuric salt causes the kidney vessels to dilate, the local blood-pressure to rise, and secretion to increase. Moreover, it is certain that mercurials in excess cause desquamative nephritis; so that it must be concluded that these preparations either stimulate or irritate the renal secretory structure proportionately to the amount present. According to Bieganski, the diuretic effect is most active after subcutaneous injections and least so after inunctions.

The destruction of renal secreting tissue by disease without doubt interferes with the diuretic action of mercurials, but the fact remains that in chronic *parenchymatous nephritis* with alarming decrease in the secretion of urine, calomel is one of the most effective diuretics known. In *cardiac dropsy* it is often very efficient in improving not only the dropsy itself but the condition of the digestive organs. In some cases of chronic cardiac disease the continued use of minute doses of the mercurial is very advantageous, but when it is desired powerfully to affect the kidneys large doses of the drug are required. Under these circumstances, we have found the administration of five grains of calomel every two hours until fifteen grains in all are taken to act most happily. It is sometimes, though rarely, necessary to use opium to check the purgative action of the calomel. When there is excessive debility some caution may be necessary in this use of mercurials, but we have seen life apparently saved for the time being by the removal of an acute *suppression of urine* in advanced *Bright's disease*.

THEOBROMINE.—Theobromine (dimethylxanthine) is a crystallizable alkaloid, which forms very bitter salts that are mostly dissolved with difficulty. The proprietary remedy *Diuretin* is a more or less impure theobromine and sodium salicylate. The pure *sodium* and *theobromine salicylate* is a white powder, soluble in less than half its weight of warm water, containing about forty-nine per cent. of theobromine: the commercial article, according to various analyses, has in it from thirty to forty-eight per cent. In 1890 the attention of the profession was called by C. Gram[13] and by Kouindig-Pomerantz[14] to the value of theobromine and sodium salicylate as a powerful and practical diuretic. The observation of Albanese, that theobromine when ingested is eliminated through the kidneys in part unchanged and in part converted into methylxanthine, has been confirmed by Bondzynski and Gottlieb.[15]

Ivan M. Sabashnikoff[16] states that the toxic dose of diuretin produces free salivation, vomiting, and diarrhœa, as well as free diuresis. The same authority affirms that the respiration is quickened by the small

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dose, whilst the large dose causes an intense dyspnœa, with elevation of bodily temperature which sometimes amounts to four degrees centigrade, but is prevented by previous high section of the spinal cord. Upon the striated muscles the action of the drug is said to be similar to that of caffeine. The Russian observer has further found that a large dose of diuretin sharply increases the irritability of the motor area of the cerebral cortex, and although under its influence the cardiac beats become first slower and then in a little while more frequent and more energetic, the arterial pressure sinks from the beginning. Cohnstein[17] also has noticed the fall of arterial pressure after the toxic dose of diuretin, but states that the ordinary dose has no perceptible influence upon the heart and blood-vessels.

Sodium and theobromine salicylate has been much used as a practical diuretic, the general professional verdict being that it has direct influence upon the renal secreting structure, that it is non-irritating to the kidneys, and that it rarely causes disagreeable symptoms. It has been especially recommended in *cardiac dropsy*, and it is asserted by various practitioners that when the heart is weak it exerts a direct and immediate influence in increasing the arterial pressure and favorably regulating the cardiac beat (Masius, also Pawinski[18]). Theobromine has also been highly commended both in very *acute* and *chronic nephritis.* In rare cases it acts unfavorably, causing headaches, irregularity of the pulse, vomiting, diarrhœa, and even—according to W. Schmieden—hæmaturia. From eighty to one hundred and twenty grains (6–8 Gm.) may be administered during the course of the day, in capsules or solution, or hypodermically. According to Demme, to a child six years old twenty to thirty grains (1.3–2 Gm.) may be given in the twenty-four hours.

Spiritus Ætheris Nitrosi. U. S.—When given in a single large dose (a teaspoonful to a tablespoonful) and the patient afterwards kept cool, sweet spirit of nitre acts as a feeble diuretic, at the same time soothing the kidneys. It is often useful when there is slightly diminished renal excretion of functional origin, or when the kidneys suffer from slight congestion, as shown by aching in the loins.

Digitalis, in its general relations, has already been sufficiently discussed, and it remains only to speak of its employment as a diuretic. In the first place, it should be distinctly understood that it has no alterative effect whatever, either upon the nature of the secretion or upon the mucous membrane over which that secretion flows. In other words, when it has any effect it is purely a hydragogue diuretic, simply increasing the watery portion of the urine. That digitalis has direct diuretic properties cannot, we think, be doubted. Nor does it seem less certain that it varies greatly in their exercise, so that when given to persons in health it will sometimes produce free diuresis and will at other times fail to do so. Another point to be constantly borne in

mind during its administration is the fact that, like all the other effects of digitalis, diuresis is very slowly induced, and is very persistent when produced by the ordinary cautious method of administration. The diuresis of digitalis is not simply a result of its action on the circulation, since it will sometimes appear before the circulation is sensibly affected. At the same time, it is very evident that in disease the good effect of digitalis upon the renal organs is often in large measure due to its action upon the heart. Thus, in dropsy from a dilated heart the renal gland-cells cannot secrete because they are not supplied with the proper kind and quantity of blood, their circulation, like that of the remainder of the body, being nearly stagnant. If under these circumstances digitalis be exhibited, and the circulation becomes comparatively free and active, the resultant diuresis is wrought out through a double mechanism, partly indirectly and partly directly produced by the drug. As a consequence of these facts, clinicians have long since practically determined that digitalis is especially valuable as a diuretic in *cardiac dropsy*. Digitalis is also very useful in *renal dropsy*, both in the subacute and in the chronic form. Of course, like everything else, it frequently fails in these varieties of Bright's disease, but certainly it should always be tried. In acute *suppression of urine* the external application of digitalis is often efficient. Flannels wrung out of the infusion, or containing an ounce of the tincture, may be applied to the abdomen and covered with oil-silk. Some practitioners prefer poultices made directly of the leaves. Lente[19] says that he has been accustomed to use, even in children, four ounces of the best English leaves, and with a quart of water "make a poultice which extends all round the body, and from the thorax to the pelvis." The application should not be left on for more than from eight to ten hours, and only in desperate cases should very large amounts be employed, as the external use of a single ounce of the tincture has caused almost fatal collapse.*

The dose of the powder of digitalis, as a diuretic, is three grains (0.2 Gm.) a day (in divided doses), increased by a grain every second or third day, until some sensible effects are manifested. The infusion or the tincture may be substituted for the powder, in corresponding dose. Digitalis, in the majority of cases, is best given in combination: in cardiac dropsy it is much more efficient if given with squill; in renal diseases the potassium bitartrate may be exhibited simultaneously.

Jaborandi, *Strophanthus*, and *Caffeine* are active, practical diuretics. (See respective articles.)

SUGAR.—In the last few years it has been affirmed by S. Meslach, Zavadsky, Germain-Sée, and other clinicians that both glucose and the sugar of milk are active hydragogue diuretics, which may often advantageously be used in the treatment of *cardiac dropsy*, *pleuritic effusions*,

* Case of E. F. Fannell (*Brit. Med. Journ.*, March, 1871).

etc., but are of little value when there is renal disease. The general testimony seems to be that the sugar of milk is the more active of the two. These sugars may be given in doses of from one to six ounces (30–180 Gm.) a day, administered in concentrated syrup or in milk. How sugar under these circumstances acts as a diuretic, or whether it has any influence upon the nervous system and circulation, is at present doubtful. According to the experiments of Albertoni, all sugars injected into the veins cause a rise of the arterial pressure by a direct stimulation of the heart. He also found that the kidneys, as tested by Roy's oncometer, become congested or swollen.

DEPURANT DIURETICS.

POTASSIUM.

PHYSIOLOGICAL ACTION.—The salts of potassium* are greatly influenced in their action upon the animal economy by the potash which they contain, the degree of the influence depending in some measure upon the activity of the body with which the metal is combined. Physiologically the various salts may be divided into the vegetable salts, including the carbonates, and the mineral salts.

With the single exception of the bitartrate, the vegetable salts of potassium act similarly upon the organism, varying among themselves almost solely in that some are more irritant than others.

The effects of the ordinary therapeutic doses of the potash salts upon the human system are not sufficiently obvious to be perceived by even the clinical observer. Only when a single dose is overwhelmingly large, or when by long-continued use there has been an accumulation of potash in the system, are there such obvious results as general muscular weakness, lowered temperature, depression of the circulation, dyscrasia, and, it may be, even excessive fluidity of the blood. Moreover, in acute poisoning with the potash salts the local irritant influence upon the alimentary canal or the kidneys usually overshadows the other phenomena. In the frog, and also in the mammal, injected into the blood or perhaps given in sufficient quantity, the vegetable salts of potassium produce depression of the circulation, fall of temperature, lessening of both voluntary and reflex movements, and finally death from cardiac paralysis. The mineral salts of potash are all of them powerful local irritants, but with

* The preparations of the alkaline metals are used in practical medicine for such different purposes that these metals are widely scattered in the present treatise. As insisted upon by Binet, however, they have much in common; dividing themselves naturally into two groups, one containing lithium, sodium, and potassium, characterized by producing general paralysis with the arrest of the heart in diastole; the second group, calcium, strontium, and barium, characterized by their tendency to produce, along with the loss of motor power, muscular contractions (especially barium), and by their arresting the heart in systole. Magnesium approaches the first group by arresting the heart in diastole, but separates itself by its extreme tendency to paralyze the peripheral nervous system. The law enunciated by Rabuteau, that there is a consistent relation between the toxicity of a metal and its atomic weight, appears not to be correct.

most of them the base plays an important part in producing the physiological effects of the whole combination.

Thus, Podocaepow[20] found that one cubic centimetre of the solution of the potassium chloride (1 to 5) would in eight minutes abolish in the frog voluntary and reflex movements, and in from fifteen to twenty minutes arrest the heart. In the mammal the effects of the drug were similar to those seen in the batrachian, but the muscular system was not so profoundly influenced.

Muscular and Nervous Systems.—Although Podocaepow believed that the paralysis of voluntary and reflex movements caused by vegetable potash salts in the frog is largely of muscular origin, the more elaborate experiments of Guttmann show that both nerve-trunks and muscles are capable of preserving their functions in the poisoned frog ; and that the shutting off of the poison from the extremity by tying its artery does not prevent the development of the paralysis in the protected leg ; so that, as Guttmann concludes, the loss of motor power is, at least chiefly, of spinal origin. This conclusion has been so far confirmed by Ringer and Morshead[21] as to show that probably all of the potash salts are depressants of the spinal cord, their power being in direct proportion to the amount of bases which they contain. Ringer and Murrell,[22] however, have demonstrated that not only the spinal cord, the brain, and the motor and sensory nerves, but the muscles themselves are attacked by these salts, all these tissues, however, being less susceptible to the influence of the potassium compound than is the spinal cord. Next to the spinal cord in susceptibility is the brain.

Circulation.—The influence of the potash salts upon the circulation is more pronounced than upon the nervous system. In regard to the action of small doses upon the circulation our knowledge is very imperfect. There is considerable testimony to show that they produce a rise in the arterial pressure.

Traube[23] asserts as the result of his experiments that, injected into the blood in doses of two or three grains, the potassium nitrate produces a fall in the pulse and a rise in the arterial pressure. Aubert and Dehn have experimented with a number of the salts of potassium, and found that, with the exception of the permanganate, they all act upon the circulation in the manner just described. It remains at present writing, however, doubtful whether the rise of pressure just spoken of is a direct phenomenon caused by potash. No dose of a potash salt ever calls forth symptoms of circulatory stimulation from the human body. Further, Podocaepow and also Aubert and Dehn affirm that the rise following the potash injection in the animal usually lasts only three minutes, and that in no case is the maximum effect perceptible for more than ten minutes. Aubert and Dehn further assert that there is no cumulative action, the repetition of small doses of the drug at brief intervals leaving no residual effect, the pressure returning to the normal after each injection, just as though no previous injection had been given. The correctness of this statement

remains doubtful, since Guttmann asserts that there is a gradual rise of pressure. It is evident that further investigation is necessary for the formation of an opinion. It is possible that the rise of pressure is due to a reflex contraction of the vessels, caused by irritation of the nerves in the blood-vessel walls, or in some other way is a secondary phenomenon. In Boltazi's experiments it was found impossible by any dose of a potash salt to increase the work of the frog's heart.*

The method by which the changes in the pulse are produced by the small dose of potash also remains uncertain. Traube affirms that if the vagi be cut after exhibition of the potash salt, the lessened pulse-rate instantly becomes rapid, and the already increased arterial pressure rises still further. The same observer also found that after section of the pneumogastrics small doses of the nitrate produced a fall in the pulse, with increased arterial pressure; but on a repetition of the dose in the same animal no lessening of the pulse-frequency was perceptible, while each time the pressure rose. This seems to indicate that the cardiac action of the drug is independent of the inhibitory apparatus, which is confirmed by the experiments of Aubert and Dehn upon atropinized dogs.

Whatever may be the action of the small dose, the large dose of the potash salt greatly and progressively lowers the arterial pressure. This fall is, in great measure at least, due to the direct action of the poison upon the heart. When a frog is killed by a salt of potassium the heart† is usually arrested in diastole (Podocaepow, Guttmann). Ten to fifteen grains of the chloride quickly injected into the jugular vein of a small mammal suffice to produce instant cardiac death. Traube states that the heart-muscle in the dog killed by the intravenous injection of the potash salt is entirely unable to respond to electrical stimulation. According to Aubert and Dehn,[24] for a few seconds before complete suspension of cardiac movements there are irregular, "stormy" convulsions, which run through the heart in a sort of peristaltic manner with great rapidity, but have no effect in expelling the blood. A curious fact discovered by Aubert and Dehn is that the effect of the potash is not permanent unless it has continued a certain length of time. Thus, a hound received into its jugular a fatal dose of potassium chloride, and ten seconds after all pulsations had ceased the crural artery of a second dog was connected with the jugular of the poisoned animal, when the heart recommenced its movements, only to cease again after a time.

The careful experiments of Podocaepow[25] and of Guttmann have shown that when the fatal poisoning is the result of a gradual introduction of the potash salt, although the contractility of the cardiac muscle is very much impaired at the time of death, it is not completely destroyed.

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* *Arch. Ital. d. Biolog.*, xxvi.

† The poisonous influence of potash upon the heart was, we believe, first discovered by Black (*Comptes-Rendus*, 1839), and has been confirmed by Bouchardat (*Annuaire de Thérapeutique*, 1844), by Grandeau (Robin's *Journal de l'Anatomie*, 1864), by Rabuteau (*L'Union Médicale*, 1871), and by others.

Section of the vagi, according to Guttmann, has no influence upon the action of the poison, and it seems to be established that the depression of the cardiac muscle is by a direct action of the salt upon the muscle itself. Dogiel[26] has shown that this action of the drug is in fact only a portion of a wide-spread general influence exerted upon all muscle-fibres, the heart-muscle being simply more sensitive to the influence of the poison than are the skeletal and intestinal muscle-fibres. It is almost certain that the fibres in the walls of the blood-vessels are also attacked, so that the fall of blood-pressure produced by the poisonous dose of potash is the outcome of a conjoint depression of the muscle-fibres of the heart and blood-vessels.*

Influence upon Nutrition.—Outside of the body, potassium favors very greatly the oxidation of organic substances. Thus, when albumin or hæmatin is dissolved in water no change, or a very slow one, occurs, but if potash be added the organic principle is oxidized with extraordinary rapidity. There is now sufficient evidence to establish the original theory of Lehman, that this oxidizing influence is exerted by these salts in the living body. The fall of temperature produced by poisonous doses of potassium salts is probably due to excessive loss of heat caused by loss of tone in the blood-vessels. That there is under the influence of the alkali a great increase of nitrogenous elimination both in health and disease seems to be fairly proved.

In an elaborate series of experiments upon himself, E. A. Parkes[27] found that liquor potassæ (two fluidrachms) when taken fasting, produced in from thirty to ninety minutes an increased flow of slightly acid urine containing the whole of the alkali and organic matter, which differed in quality from that ordinarily found in urine, and was also larger in amount than normal. An organic acid, certainly neither uric nor hippuric, was believed to form a part of the solid matter by Parkes, who attributes the alteration of the urinary solids to the oxidizing influence of the potash. Taken after meals, the liquor potassæ acted simply as an antacid, and had no perceptible effect upon the urine. Both potassium acetate and nitrate in Parkes's experiments failed to act on the urine, probably because taken in too small doses, for it is a fair presumption that their oxidizing influence is less than that of potash itself. Certainly other experimenters have determined that they do influence the urinary excretion. Golding Bird[28] found that in a case carefully tested, under favorable circumstances, three drachms of potassium acetate increased the solids of a dog's urine from four hundred and sixteen to seven hundred and eighty-two grains, or, deducting all the eliminated potash, to over six hundred grains. The increase of the uric acid was about thirty-two per cent.; of the urea, about sixty per cent.; of extractives, including kreatine, kreatinine, etc., about twenty per cent.; or, speaking absolutely, the uric acid was increased eighty-five grains, the urea seventy-two grains, and the extractive thirty-six grains. Rabuteau[29] found that the daily ingestion of seventy-five grains of potassium chloride caused an increase of twenty per cent. in the amount of urea discharged. Aug. Dehn[30] has also experimentally found that the potassium salts greatly increase the elimination of urea.

* Ringer and Murrell, applying the potassium, ammonium, and sodium chlorides, iodides, and bromides directly to the ends of the afferent nerves, found that they paralyzed, the effect of the potassium being much the most powerful and permanent, that of ammonium the next, and that of sodium the least (*Journ. Anat.*, xii. 71).

The conclusion reached by experimental research made upon healthy men and animals—namely, increased tissue-change as the result of potash ingestion—is in close concord with those upon diseased organisms.

In six observations upon subjects affected with what may be termed indifferent diseases, such as lead palsy, Parkes[31] found that the urea was increased, and also the sulphuric acid, by the use of drachm doses of liquor potassæ. Austin Flint[32] has studied the effect of potassium nitrate upon a number of persons suffering from various diseases, and found that it very greatly increases the amount of solids in the urine. In rheumatism Parkes found that liquor potassæ increased the elimination of sulphuric acid, but had no decided influence on the uric acid. He, however, used such small doses of the drug as not to get the effect obtained in the alkaline treatment of the disease, since he expressly states that the urine remained acid. Rheumatism, gout, and the uric acid diathesis certainly bear some relation with one another. It has long been customary to use potash salts in excess of uric acid in the urine, and the relief obtained has been believed to be due to the conversion of the acid into a urate. Basham[33] affirms, however, that as the result of a series of analyses he has found that in uric acid diathesis not only is there a great increase of the urea during the use of potash, but also that the uric acid, either free or combined, in the urine is greatly diminished. Basham, remembering that Schunck had proved that, under the oxidizing power of potash, uric acid outside of the body is converted into oxaluric acid, which in its turn is readily metamorphosed into oxalic acid and urea, carefully examined the urine of gouty patients taking the alkali, and found that not only was the urea increased, but that oxalic acid also appeared as the uric acid decreased, and that the urine, on standing, deposited crystals of calcium oxalate, although none of these could be found in it when first voided. This research of Basham certainly seems to demonstrate that in uric acid diathesis the potassium salt increases the oxidation and the ultimate metamorphosis of tissue.

Rabuteau, in his experiments with potassium chloride, found that the urine maintained its acidity, although potassium acetate, carbonate, or citrate produced alkalinity of the urine. A plausible explanation of this diversity is that the vegetable acid salts are oxidized into carbonates in the system, while mineral acids of necessity pass through unaltered. Thus, from the urine of a patient taking two hundred and seventy grains of the nitrate daily, Alfred S. Taylor[34] obtained 158.7 grains of the ingested salt per diem.* If, as there is much reason to believe, a vegetable acid when given alone passes through the system in great measure unchanged, while, as asserted by Münch,[35] and as seems to follow from the facts already brought forward, the same acid is found when combined with an alkali to be oxidized and converted into carbonic acid, there is in this strong corroboration of the belief that the *potash salts increase oxidation in the system.* Putting all the evidence together, it seems to us that the oxidation theory must be accepted as exceedingly plausible and probable, although not, perhaps, absolutely proved.

* A portion of the potassium salts escapes through the intestines, as Kramer (*Annales d' Hygiène Publique et de Méd. Lég.*, 1843, i.) has found the nitrate in the fæces of animals taking it; and it is much more probable that the nitrate not accounted for in Taylor's investigation was eliminated by the intestines than that it was decomposed in the system.

When a potassium salt is given in large doses for a long time, it produces a condition of dyscrasia, with impoverishment and excessive fluidity of the blood. It is probable that there is some connection between these changes and the oxidizing power of the drug.

POTASSII CARBONAS. U. S.—*Potash* of commerce, obtained from wood-ashes and other sources, occurs in the form of fused, stony masses, variegated in color, and of a caustic, burning taste; when purified so as to form *pearlash*, it becomes of a bluish-white color. When further purified so as to conform with the official tests, it occurs as a coarse, granular, whitish powder, very deliquescent, soluble in its weight of water, insoluble in alcohol. It is too irritant for use as an internal remedy.

POTASSII BICARBONAS. U. S. — *Potassium Bicarbonate* occurs in transparent, colorless crystals, not deliquescent, slightly alkaline to the taste and to test-paper. It dissolves in 3.2 parts of water at 59° F., but is insoluble in alcohol. This salt may be used as an antacid or to increase the liquidity of the bile, as in *catarrhal jaundice*, but it is so disagreeable to the taste that the acetate or citrate is much preferable when free continuous medication of the general system is desired. Dose, as an antacid, fifteen to thirty grains (1–2 Gm.), in dilute solution.

LIQUOR POTASSÆ. U. S.—*Solution of Potassa* is a colorless, water-like liquid, of a strong, acrid, alkaline taste, and is made by boiling a solution of the potassium bicarbonate with lime. It contains only five and eight-tenths per cent. of the alkali, but is capable, in overdose, of acting as an irritant poison. Dose, ten to twenty minims (0.6–1.2 C.c.), well diluted.

POTASSII CITRAS. U. S.—*Potassium Citrate* is a whitish, granular, deliquescent salt, of neutral or very slightly acid reaction, freely soluble in water. It is the least offensive to the palate of all the potassium salts, except the tartrates. The *Solution of Potassium Citrate* (LIQUOR POTASSII CITRATIS, U. S.,—potassium bicarbonate, one hundred and twenty-three grains; citric acid, ninety-two grains; water, three fluidounces) and the *Neutral Mixture* (MISTURA POTASSII CITRATIS,—lemon-juice, one pint; potassium bicarbonate, enough to neutralize) have been long used as diaphoretics in sthenic *fevers*. The dose is half a fluidounce to one fluidounce (15–30 C.c.) every one or two hours. A very elegant method of exhibiting neutral mixture is in the form of *Effervescing Draught*. It is especially useful when there is any tendency to sick stomach. It should be prepared in two solutions: one consisting of lemon-juice and water, equal parts, or of citric acid two drachms, water four fluidounces; the other of potassium bicarbonate one drachm, water three fluidounces. An ounce (30 C.c.) of each of the solutions is to be put together and drunk during effervescence.

POTASSII ACETAS. U. S.—*Potassium Acetate* is a perfectly neutral white salt, of a decidedly saline taste, extremely deliquescent, and soluble in half its weight of water. It is made by dissolving the bicarbonate in acetic acid, and evaporating. It occurs sometimes as soft, fibrous masses, at other times it has a foliated structure.

THERAPEUTICS.—An important use of the vegetable salts of potassium is in *acute inflammatory rheumatism*. Before the introduction of the salicylates the alkaline treatment was the best that was known for cases of thoroughly acute *rheumatism:* the medicine must be given freely, an ounce to an ounce and a half in the day, and be persisted in; opium, of course, being at the same time employed in as large doses as are required to relieve the pain: after a few days, when the violence of the symptoms has abated and decided anæmia appears, the exhibition of the drug should be discontinued and potassium iodide, with tonics, be substituted. In cases subacute from the beginning a combination of the potassium iodide and acetate is sometimes very efficient, ten grains of the former and thirty of the latter being administered three or four times a day. The potash probably does good in rheumatism by lowering arterial action, by favoring oxidation and elimination of partially effete materials, and by neutralizing excessive acidity.

As depurants, the potash salts are very useful in various diseases. Attention has been especially called by Golding Bird to their value in that class of cases spoken of as *chronic biliousness*. In chronic *malarial poisoning*, in *catarrhal jaundice*, and in the *jaundice* of simple *hepatic torpor* they are often of use. In *uric acid gravel* and in *uric acid calculus* the vegetable salts are useful in checking the deposition of the uric acid, but have no influence upon calculi already formed.

ADMINISTRATION.—As usually exhibited, the potash salts are exceedingly distasteful. There is no need of this whatever. The citrate may be given dissolved in lemon-juice, or, what is a still more pleasant method, a syrupy solution of the bicarbonate and the citrate may be made, of such a strength that every tablespoonful of it shall contain half a drachm of each salt. At the time of exhibition one or two tablespoonfuls of this may be put in a little water, and to it be added a large tablespoonful of lemon-juice, the whole to be drunk while effervescing. If the patient takes in the course of the day six of the largest doses mentioned, the whole amounts to an ounce and a half of potassium citrate. When the remedy is used simply as a depurant, as in jaundice, such large doses are, of course, not proper; a teaspoonful of the alkaline solution, with a corresponding amount of lemon-juice, taken three times a day, will generally be sufficient.

POTASSII BITARTRAS. U. S.—*Potassium Bitartrate* occurs in white crystalline crusts or masses, which are commonly pulverized before being sold as *Cream of Tartar*. It usually contains calcium tartrate, and is only sparingly soluble in cold water. It is probably eliminated unchanged

as a bitartrate, and certainly differs from its congeners in being an active hydragogue diuretic and cathartic. Half an ounce to an ounce (15–30 Gm.) of it given at once will very generally cause watery purging. An ounce (30 Gm.) of it in a pint of infusion of juniper-berries, taken, in divided doses, during the twenty-four hours, will very often act most happily in *dropsy*. In acute *desquamative nephritis*, cream of tartar is often very serviceable; as, however, the avoidance of irritation of the kidneys is imperative in this disease, the infusion of juniper should not be used.

POTASSII SULPHAS. U. S.—*Potassium Sulphate* occurs in small aggregated, transparent, very hard crystals, permanent in the air, usually short six-sided prisms, possessing a nauseous somewhat bitter taste. It is said to be, in doses of four or five drachms, "a mild purgative, operating usually without heat or pain or other symptoms of irritation," and in doses of one or two drachms a laxative. It is, however, a powerful irritant, and we have never seen it administered. Mowbray states that the salt is used in France as a popular abortifacient, and that he has seen very alarming symptoms produced by four drachms of it. Two ounces have caused a fatal gastro-enteritis (Taylor).

POTASSII NITRAS. U. S.—*Potassium Nitrate*, or *Nitre*, is ordinary saltpetre. *Chili saltpetre* has no physiological similitude with true saltpetre, being a *sodium nitrate*.

Saltpetre occurs in more or less perfect, long, striated, semi-transparent, six-sided prisms, with dihedral summits; of a sharp, saline, somewhat cooling taste; containing no water of crystallization, but decrepitating when thrown on the fire, from the evaporation of water mechanically retained in the crevices of the crystals; soluble in four or five times its weight of cold and in two-fifths of its weight of boiling water, sparingly soluble in proof spirit, insoluble in absolute alcohol.

PHYSIOLOGICAL ACTION.—Potassium nitrate is so violently irritant that the general effects of the potash in it upon the system are lost in the local symptoms caused by its overdose. If by very free dilution the local irritant influence of the nitre be overcome, the poison loses much of its virulence and extraordinary amounts can be taken without serious results.*

The symptoms of poisoning by potassium nitrate are an intense burning pain in the stomach, coming on in a few minutes after the ingestion of the poison, and soon followed by violent vomiting, and, it may be,

* In a case under the care of Wilks (*Guy's Hosp. Rep.*, 3d series, 1863, ii. 173), a man suffering from renal dropsy took, between October 28 and December 26, 1862, one pound twelve ounces and six drachms of potassium nitrate, with benefit. As one ounce has caused death in three hours (Taylor, *Medical Jurisprudence*, 2d ed., i. 237), this patient received in fifty-nine days the equivalent of twenty-eight fatal doses. Again, according to Stillé (*Therapeutics*, ii.), Brocklesby habitually prescribed one ounce of the salt a day, and Martin-Solon even two ounces per diem.

free purging, with, after some hours, collapse, great muscular weakness, and not rarely local convulsive tremblings. The matters vomited, and even the stools, may be bloody (Husemann[36]). Sometimes the nervous symptoms predominate, and the purging may be absent: collapse, with slight vomiting and with or without paralysis of the lower limbs, may alone exist. Suppression of urine has been noted in some cases.* After death, very grave lesions are found in the stomach and the intestines, such as intense redness and congestion, and effusion of blood into the submucous coat, and sometimes into the stomach itself. Even ulceration and corrosion of the mucous membrane have been observed. How far potassium nitrate acts upon the blood is at present uncertain; Mairet and Combemale assert that it alters the red blood-corpuscles. Sometimes, however, death has occurred, in poisoning by saltpetre, with great suddenness. In the only cases of this character the record of which we have read the dose has been very large, and it is possible that the death has been the result of the paralyzing action of the potash upon the heart.

Potassium nitrate is of no value as an internal remedy, having been superseded by the vegetable salts in *acute rheumatism*. Its local action is very similar to that of the chlorate.

In the treatment of poisoning by saltpetre, after the stomach and bowels have been emptied, the usual means for the relief of toxic gastro-enteritis should be resorted to.

Potassii Chloras. U. S.—*Potassium Chlorate* occurs in white rhomboidal plates of a pearly lustre and of an acerb taste, soluble in seventeen parts of water at 59° F., and in two parts of boiling water.

Physiological Action.—Locally, this salt is a very active stimulant and irritant. As a poison it has frequently caused death.† The smallest fatal dose is not known, but half an ounce has killed. A drachm taken during a night has killed an infant a year old, and three drachms a child three to four years old. The symptoms may be acute or subacute. In the rapid cases there have been violent vomiting, profuse diarrhœa, excessive dyspnœa, great failure of the heart's action, and marked cyanosis. In the subacute cases the gastro-intestinal symptoms have been severe, with generally vomiting of blackish-green matters and distinct swelling of the liver and the spleen. The urine is markedly lessened in quantity, albuminous, often of an opaque reddish-brown or blackish color, and showing under the microscope brownish or yellowish-brown tube-casts, frequently containing the detritus of blood-corpuscles. Hæmoglobinuria has been noticed,‡ and methæmoglobin is a common constituent. The

* Case, *Pharmaceut. Journ.*, Feb. 1846, 356.

† For collection of cases, see *Chlorsäure Kali*, J. von Mering, Berlin, 1885. To Jacobi, of New York, belongs the credit of having first called attention to the dangerous action of this much-abused remedy (*American Med. Times*, April, 1861, 245).

‡ *Trans. Internat. Congress*, 1881, I. 463.

potassium chlorate is reduced in the system, chiefly because he thinks that methæmoglobin is formed by a process of oxygenation. The exact nature of methæmoglobin is, however, not made out; according to C. A. Macmunn,[44] methæmoglobin is probably a mixture of hæmatin with soluble albumin, Hoppe-Seyler having shown that it is not a result of oxidation.

Von Mering in one or two instances in the dog found a slight increase in the chlorides of the urine during the administration of the chlorate, and it is possible that a minute quantity of the chlorate does undergo deoxidation; but it must be considered established that any such change, if it occurs at all, affects so small a portion of the drug as not to be worthy of consideration.

The therapeutic dose of potassium chlorate produces no sensible effects in the system. Isambert found that, when taken by himself in doses of from two to five drachms, it caused salivation, free diuresis, increase of the appetite, and, when not well diluted, gastric irritation; the urine continued strongly acid, and contained an excess of rosacic acid, uric acid, and the urates.

THERAPEUTICS.—Largely on account of the groundless belief that it favors oxidation of the blood, the profession has in the past used potassium chlorate in many forms of disease believed to be due to blood-poisoning. There is, however, no scientific or clinical reason for believing that the drug has any value whatsoever in these or other diseases, except through its local action, and without doubt its free use in *diphtheria* has often greatly aided in the production of a fatal result, its irritant action upon the kidneys making it a dangerous remedy in that disease. On the other hand, it is a very valuable local remedy, especially in diseases of the mucous membrane of the mouth. In the *follicular* or *aphthous stomatitis* of children * it is almost a specific, its free elimination with the saliva causing it to be constantly present in the mouth, even when taken intermittently. Its local influence, however, is too feeble to be effective in such serious diseases as *diphtheria*. In ordinary *sore throat* or *angina* the combination of it with the fluid extract of sumach-berries is as a gargle most effective.

In chronic *dysentery* and other diseases of the colon it may be applied by means of the large enemata. In *hemorrhoids* the injection, when the patient goes to bed, of half to one ounce of its saturated solution, combined with a few drops of laudanum to secure retention, is often of the utmost service. In *stomatitis* and allied diseases powders of potassium chlorate, ten to fifteen grains (0.6–1 Gm.) each, should be put dry in the mouth every three to six hours, so as to secure the maximum of local action.

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* Laborde (*Bull. Thérap.*, 1874, lxxxvii.) and Tacke (*Inaug. Diss.*, Bonn, 1878) have shown that *sodium chlorate* acts physiologically like the potassium salt; and S. Ringer and H. Sainsbury (*London Lancet*, 1882, ii. 736) have found it equally efficient in *stomatitis*.

LITHIUM.—Our knowledge of the physiological action of the lithium salts is very slight. None of the official salts are distinctly irritant; they are all of them rapidly absorbed and rapidly eliminated through the kidneys, the carbonate and the citrate probably as alkaline carbonates, giving the alkaline reaction of the urine. No cases of poisoning by them appear to be on record, but we have seen large repeated doses cause malaise with excessive muscular weakness.

According to the studies of Binet,[45] the lithium salts produce in mammals pronounced feebleness, with nausea, diarrhœa, and other digestive disturbance, increasing dyspnœa, fall of temperature, and death, usually preceded by convulsions. Death is said to be due to a direct centric arrest of respiration, although a markedly depressing influence is exerted upon the heart, which is finally arrested in diastole. When life is maintained by artificial respiration the peripheral nerves become entirely paralyzed and the muscles affected, as is shown by peculiar fibrillary contractions. In poisoned frogs, also, the excitability of the muscles is somewhat diminished.

It is probable, though not proved, that the lithium salts are depurative, increasing the elimination of effete materials through the kidneys. Originally recommended by Ure and Garrod, especially on account of their power of dissolving uric acid and the urates, they have established themselves as of some value in *uric acid diathesis* and chronic *gout*. Their influence is limited, but as a minor remedy they are often serviceable in chronic cases in doses of from five to fifteen grains (0.3–1 Gm.), given after meals. E. Duché[46] affirms that their prolonged local application is very useful in relieving *gouty joints*, and that in gouty *conjunctivitis* frequent washing of the eye with a solution of lithium carbonate, 1 to 500, is effective.*

The U. S. Pharmacopœia recognizes *Lithium Benzoate* (LITHII BENZOAS, U. S.), a white powder, soluble in four parts of water; *Lithium Carbonate* (LITHII CARBONAS, U. S.), similar in appearance, but sparingly soluble in water, five to fifteen grains (0.3–1 Gm.); *Lithium Citrate* (LITHII CITRAS, U. S.), a white deliquescent powder, soluble in two parts of water, ten to thirty grains (0.6–2 Gm.); also the *Effervescent Lithium Citrate* (LITHII CITRAS EFFERVESCENS, U. S.), a white powder, each one hundred grains of which contains seven grains of lithium carbonate, twenty-eight grains of sodium bicarbonate, and thirty-seven grains of citric acid. When added to water it effervesces freely and affords the most pleasant means at our command of exhibiting an alkaline salt of lithium. The *Lithium Bromide* (LITHII BROMIDUM, U. S.) is used simply as a bromide.

* *Martineau's Solution.*—Martineau affirms that he has obtained very remarkable results in the treatment of *diabetes mellitus* by the use of a solution of lithium carbonate and sodium arsenate. In gouty diabetes this *arsenical solution of lithium* may prove of service: from five to ten grains of lithium carbonate and one-thirtieth of a grain of sodium arsenate may be given three times a day.

PIPERAZINE.—*Piperazidine*, or *Diethylendiamine*, occurs in small, glassy, lustrous tables, or, in the form of the *hydrochlorate*, in silky, lustrous, lanceolate crystals. It has been used as a solvent for uric acid, one part of which with one part of piperazine will dissolve in fifty parts of water. It has also been alleged that it will dissolve the albuminous substances which form an important part of uric acid calculi. Undoubtedly, however, it will not dissolve an already formed calculus in the human bladder, though it may sometimes be of service as a solvent in uric acid gravel.

Piperazine is rapidly absorbed and eliminated through the kidneys, producing a reddish-brown urine. Concerning its general physiological action there is very little knowledge. The therapeutic dose produces in man ordinarily no symptoms, but we have seen muscular weakness and general depression follow the continuous exhibition of large doses. Whether it does or does not affect the general nutrition is unknown. Vogt asserts that it checks uric acid elimination. Ebstein and Sprague have found that it has no effect either upon the excretion of urea or of uric acid. It has been very largely used in *gout*, but has failed to sustain its first reputation, although in occasional cases it apparently exerts a markedly beneficial influence for a time. It causes too much pain to be used hypodermically ; fifteen to twenty grains (1–1.3 Gm.) of it may be administered by the mouth, during the day, in a quart of plain or carbonated water. It is too hygroscopic and too easily decomposed to be given in powder or in watery solution, but the solution of one part in twenty of alcohol and eighty of water is said to be fairly permanent. Van der Klip has found that in the lower animals, in sufficient dose, it produces vomiting, irregular breathing, general muscular weakness, and relaxation ; that it decreases the oxidizing power of oxyhæmoglobin and the coagulability of the blood ; and that it checks the action of peptonizing ferments.*

UROTROPIN.—*Hexamethylenetetramine.—Formin.*—This substance occurs in rhomboidal, very soluble crystals, odorless, and of a sweet, bitterish taste. In the presence of acid it breaks up into formaldehyde and ammonia, and, according to A. Nicolaier, is also decomposed by alkalies at a high temperature.

PHYSIOLOGICAL ACTION.—*Local Action.—Absorption and Elimination.*—Locally, urotropin is irritant. It is absorbed with great rapidity and is eliminated freely from the kidneys at least in part unchanged, its presence in the urine being usually demonstrable within half an hour after its ingestion. Nevertheless, the theory first brought forward by Loebisch,[47] that it is decomposed in the system with a setting free of

* H. Hildebrandt (*Berlin. Klin. Wochen.*, 1894) having found that piperazine, even in small quantities, checks the saccharifying influence of hæmic and other hydrolytic ferments, although it has no destroying influence, tried the drug in diabetes produced in dogs by phloridzin with pronounced success ; so that the remedy is certainly worthy of trial in *diabetes mellitus*.

formaldehyde, has received confirmation at the hands of Casper,[48] who states that he has found formaldehyde in the blood of a rabbit into which he had injected urotropin hypodermically, and has also been able in some cases to detect formaldehyde in the urine of persons taking urotropin, though in other cases no formaldehyde could be made out. It is, therefore, probable that urotropin is to some extent decomposed in the system. An observation of Casper, that formaldehyde is given forth for days by the urine of persons who have taken urotropin, indicates that the urotropin undergoes decomposition in the urine itself after its secretion by the kidneys.

General Effects.—The ordinary therapeutic dose of urotropin produces no general symptoms, and we know of no cases of poisoning by it. In the dog the daily dose of two hundred and eighty grains is said to cause no other disturbance than renal irritation (Nicolaier). The ingestion of one hundred and twenty grains a day of it usually causes in man burning pain in the bladder and urethra, especially after urination, followed, if the dose be continued, by the appearance of albumin, red blood-corpuscles, and abundant renal epithelium in the urine.

THERAPEUTICS.—Urotropin was especially brought forward by Bardet[49] and Laquers as a solvent for uric acid, but, according to the experiments of Arthur Nicolaier,[50] it is *less* active in this respect than is piperazine, and is of no practical value for the solution of renal calculi. On the other hand, it ranks with piperazine as useful in uric acid diathesis, and is especially valuable as an alterative diuretic in the treatment of *pyelitis*, *cystitis*, and *ammoniacal phosphaturia*. In *gonorrhœa* it has failed to be of service. A. Citron[51] believes that, as the good obtained in diseases of the genito-urinary tract depends upon the liberation of formaldehyde in the urine, it is essential to maintain acidity of the urine during the administration of the urotropin, the decomposition of the urotropin not occurring at the temperature of the body in the presence of alkalies. Dose, seven and a half to fifteen grains (0.5–1 Gm.), three or four times a day, in a half-pint of water.

STRONTIUM.

Although the contrary had been stated by Thomson in 1818, by Vulpian in 1885, and by Gautier in 1886, the strontium salts were generally believed to be violently poisonous until in 1891 J. V. Laborde[52] pointed out that this reputation was due to the fact that the commercial strontium salts were contaminated with the violently poisonous barium salts, and further affirmed that the chemically pure strontium salts were innocuous unless in very large doses.

Absorption and Elimination.—As was first determined by Horatio C. Wood, Jr.,[53] and afterwards confirmed by H. C. Wood and John P. Arnold,[54] when an official strontium salt is given by the mouth it in great part escapes from the intestines unabsorbed; only a minute quantity of it, often not more than a trace, being thrown out from the kidneys, and a

large proportion of it being recoverable from the fæces. The soluble strontium salt is immediately decomposed, in whole or in part, by the hydrochloric acid in the stomach, and that which escapes into the intestines is evidently precipitated by the alkalies and phosphates in the enteric fluids. Given hypodermically, the soluble strontium salt is very slowly and very imperfectly absorbed. When administered continually by the mouth, absorption goes on very slowly but persistently from the alimentary canal; but even under these circumstances the amount of strontium taken into the system is very small, so that it is extremely difficult to produce any constitutional effects.

The reason that strontium so frequently is subordinate to the substance with which it is combined is to be found not chiefly in its comparative inertness, but in the difficulty with which it is absorbed. In the experiments of Wood and Arnold it was found that when a solution of strontium salicylate was added to the 0.1 per cent. solution of hydrochloric acid practically all of the salicylic acid is at once set free. Also, that when strontium salicylate is given to man the urine in an hour contains much of the acid, but only a trace of the base. As the 0.1 per cent. hydrochloric acid solution is considerably less acid than is normal gastric juice, it is evident that the strontium salicylate is at once decomposed in the stomach, and that the strontium acts almost solely as a carrier. There is reason for believing that the strontium is a feeble antiseptic, and that when in the alimentary canal it acts favorably upon the digestive glands and muscles, so that in the case of the official salts, strontium bromide, strontium iodide, and the non-official strontium salicylate, the base is useful as a carrier which yields the substance with which it is in combination to absorption and at the same time improves digestion. How far the clinical results which have been obtained from the use of the strontium lactate are due to the strontium and how far to the lactic acid is at present uncertain.*

PHYSIOLOGICAL ACTION.—So far as we are aware, there are no cases on record in which any distinct symptoms have been produced in man by the strontium salt unless the substance with which the strontium was combined was sufficiently active to make itself manifest. Binet affirms that the continuous use in the lower animals of excessive doses produces general feebleness with increasing dyspnœa, cyanosis, clonic convulsions, and death from asphyxia. When recovery occurs the motor power gradu-

* That the effect of strontium is often subordinate to that of the substances with which it is combined is abundantly proved. Thus, in the experiments of Laborde a certain dose of strontium bromide caused localized anæsthesia with a rapid development of somnolence deepening into stupor, with marked lessening of reflexes; followed, if the dose had been large enough, by collapse, coma, and complete loss of reflex activity; whilst a similar dose of strontium chloride produced no sensible effect. The presence of strontium phosphate in bone-ash is affirmed by some and denied by other chemists. According to the experiments of Max Cremer, the feeding of strontium phosphate to young hounds has no influence in preventing the development of rickets (*München. Med. Wochen.*, 1892).

ally returns, with stiffness, ataxic movements, and not rarely with the assumption of bizarre positions. In an elaborate series of experiments by Horatio C. Wood and John P. Arnold it was found that the intravenous injection of the strontium lactate or nitrate will produce in the lower animals a marked progressive lessening in the pulse-rate, with a notable increase in the arterial pressure; the diastolic pauses becoming so long and the cardiac beats so powerful that in the dog the pulse-waves may extend over as much as eighty or ninety millimetres. If the dose has been repeated, or if it has been sufficiently large in the beginning, the pulse-waves after a time become very quick and the arterial pressure falls, although it may not reach the normal; finally, after a toxic dose, both pulse-rate and pressure at last gradually fall to zero. It was found that section of the spinal cord high up does not prevent the rise of the arterial pressure produced by the strontium salt; and that, therefore, this rise must be due to an action exercised upon the heart itself or the blood-vessel walls.

It was further demonstrated by Wood and Arnold that the strontium salts increase the cardiac energy in the isolated frog's heart and also cause contraction of the blood-vessels by a local action upon their walls; and that, therefore, the circulatory phenomena spoken of are partly the outcome of cardiac stimulation and partly caused by contraction of the vessels, the final fall of the arterial pressure being due to the stimulation passing over into paralysis. As was pointed out some time ago by Lauder Brunton, strontium affects directly the muscles; and it was found by Wood and Arnold that the extremely minute dose of strontium at first markedly increases the height of the muscle-curve and widens out its base; so that the drug primarily increases muscular power and prolongs the contraction period; later, there was muscular paralysis under the continuing influence of the poison. Experiments upon the frog's heart showed that the strontium salt has exactly this influence upon the heart, so that evidently strontium *is a muscle-poison which first stimulates and afterwards paralyzes the muscle-fibres, acting both upon the muscles of the skeleton and upon those connected with circulation;* its stimulating effect upon the circulation being, therefore, the result of a wide-spread general influence of the drug upon the muscle-fibres both of voluntary and involuntary life. It is probable, though not proved, that the muscle-fibres in the intestines are also affected by the strontium salt.

According to Binet,[55] in poisoning by strontium, the nerve-centres are more powerfully affected by the drug than are the muscle-fibres themselves, death occurring in the frog from centric respiratory paralysis; the peripheral nerves and the muscles, although depressed, still retaining after death some functional power.

STRONTII LACTAS. U. S.—*Strontium Lactate* occurs as a white granular powder, or in crystalline nodules. It is odorless, of a slightly bitter saline taste, permanent in the air, and soluble in about four parts of

water ; also soluble in alcohol. According to Germain Sée, Paul, Dujardin-Beaumetz, and other French clinicians, it is a valuable remedy in the treatment of chronic *Bright's disease*, increasing the amount of urine, diminishing or arresting the excretion of albumin, and improving the general nutrition. In albuminuria due to pulmonary congestion the drug is said to be of service, and it is further affirmed that its influence for good is especially marked in *desquamative nephritis* and much less pronounced in *interstitial nephritis*. In many cases there is no increase in the flow of urine, and the good achieved seems to be due to an alterative influence upon the secreting structure of the kidney. In our own experience the strontium lactate has not yielded results such as are ascribed to it by the French observers. It is, however, a harmless remedy, whose use should not prevent the administration of other appropriate drugs. The usual dose is from twenty to thirty grains (1.3–2 Gm.), given three times a day in solution ; but much larger amounts have been exhibited without producing apparent symptoms.

ALTERATIVE DIURETICS.

BUCHU—BUCHU. U. S.

The leaves of Barosma betulina and crenulata, natives of Southern Africa. These leaves are an inch or less in length, from three to five lines broad, of various forms, but always notched on the edges, and having a strong, rather rank, yet somewhat aromatic odor, and a warm, bitterish taste. They owe their virtues, which they yield to water and to alcohol, to a volatile oil and a bitter extractive.

THERAPEUTICS.—Buchu is a mild stimulant and alterative to the mucous membrane of the genito-urinary organs : useful in *subacute* and *chronic cystitis*, *chronic pyelitis*, and *irritation of the bladder*. Its oil is undoubtedly absorbed, and is eliminated by the kidneys, to whose secretion it imparts its odor. In *irritated bladder*, when the urine is highly acid, and when there is a constant desire to urinate, with but little relief from micturition, buchu, in combination with a vegetable salt of potash and the sweet spirit of nitre, often gives great relief. The dose of the fluid extract (EXTRACTUM BUCHU FLUIDUM, U. S.) is a teaspoonful (4 C.c.), well diluted, from four to six times a day.

PAREIRA. U. S.—*Pareira Brava* is the root of Chondodendron tomentosum, a climbing plant of South America. There appear to be in the root one or more alkaloids.* Pareira Brava has been used with asserted advantage in *cystitis*, in *irritable bladder*, and in *chronic gonorrhœa*, and appears to exert a stimulant action upon the mucous membrane of the whole genito-urinary apparatus. The doses of the infusion (one ounce to one pint) and of the fluid extract (EXTRACTUM PAREIRÆ

* See *U. S. Dispensatory*, 15th ed., 1085.

FLUIDUM, U. S.) are respectively a wineglassful (62 C.c.) and a teaspoonful (4 C.c.), four or six times a day.

UVA URSI. U. S.—*Bearberry* is the leaves of Arctostaphylos Uva Ursi, a low evergreen shrub, indigenous to northern maritime Europe, and also to our northern coasts as far south as New Jersey. They are from half an inch to an inch in length, wedge-shaped, thick, coriaceous, with a smooth, rounded margin. The odor is hay-like, the taste bitterish, astringent, and somewhat sweetish. Uva ursi contains gallic acid, besides *arbutin*, which occurs in long acicular colorless crystals, freely soluble in water, less so in alcohol and in ether, and is resolved by the action of sulphuric acid into glucose and *hydrochinone*.

THERAPEUTICS.—Uva ursi is capable of acting as a weak astringent, but has been long used in medicine for its influence upon the genito-urinary mucous membrane, and at present is employed only in chronic *pyelitis*, *cystitis*, and other affections of the genito-urinary mucous membrane, when a slightly stimulant and an astringent action is desired. Hughes found that in doses of one grain *arbutin* is a powerful diuretic. It seems to be free from poisonous properties, as Jablonowski[56] took in forty-eight hours eighteen grammes of it without discomfort. It produces a discoloration of the urine varying from pale greenish to dark greenish brown, the color deepening upon standing. It has been proved by the researches of Von Mering,[57] of L. Lewin,[58] and of Steffen[59] that the discoloration of the urine is due to the breaking up of the arbutin in the body into glucose and hydrochinone. The change probably occurs in the kidneys, as arbutin is free from toxic properties, while Brieger has shown that hydrochinone is poisonous, producing in man giddiness, ringing in the ears, lessening in the force and frequency of the pulse, etc. The experiments of Lewin indicate that arbutin is the active principle of uva ursi, and Forster[60] has shown that hydrochinone* is a powerful dis-

* According to the experiments of Brieger, *hydrochinone* produces in man giddiness, ringing in the ears, and lessening in the force and frequency of the pulse. In the experiments of P. J. Martin (*Therap. Gaz.*, 1887, 289), it caused in the frog violent convulsions, followed by paralysis and death through failure of the respiration, both convulsions and paralysis being the result of a direct influence upon the spinal cord. Small doses produced in the mammal increase of the arterial pressure, which, if the dose were sufficient, was followed by a depression. When the vaso-motor system was paralyzed and the heart isolated from the central nervous system, the effect of hydrochinone on arterial pressure was scarcely perceptible: so that it is probable that it chiefly affects the vaso-motor system. The bodily temperature is lowered by large doses of hydrochinone. According to the experiments of Martin, this is mainly due to an increase of heat-dissipation, and is, therefore, probably the result of a vaso-motor paralysis. H. G. Beyer, after experimenting upon the frog and terrapin (*Amer. Journ. Med. Sci.*, April, 1886), came to the conclusion that hydrochinone affects both the heart and the vessels as a paralyzant, lessening the rate of the heart and the amount of work done, and causing dilatation of the arterioles. Antaeff has found that if two per cent. of hydrochinone be added to fresh urine the latter will remain for many days without undergoing alkaline fermentation, but that if hydrochinone be added to a solution of urea a rapid decomposition of the urea occurs, which Antaeff believes to be the result of a direct chemical action of hydrochinone or urea (*Lancet*, April, 1887).

infectant and antiferment. It is stated that a one per cent. solution will arrest putrefaction and alcoholic fermentation, while one-half per cent. is sufficient to check butyric fermentation. Concerning the therapeutic value of arbutin there has been much discussion, but the fact that it has failed to come into general use indicates that it has little practical effect, and that H. Laurentz[61] was right in asserting that uva ursi is of value in genito-urinary diseases, chiefly on account of its tannic acid and of the volatile oil which it contains. Whatever may be the value of arbutin, it is evident that the solid extract (EXTRACTUM UVÆ URSI, U. S.) fully represents the drug, of which it is about four times the strength. It may be given in drachm (4 Gm.) doses three or four times a day. The dose of the fluid extract (EXTRACTUM UVÆ URSI FLUIDUM, U. S.) is two to four fluidrachms (7–15 C.c.), three to four times a day.

CHIMAPHILA. U. S.—*Pipsissewa* is the dried leaves of Chimaphila umbellata, a little indigenous perennial, distinguished from its inert congener C. maculata by the uniform glossy green of its leaves. The latter are about an inch and a half long, wedge-shaped, notched, pointed, and coriaceous. They contain tannic acid, bitter extractive, and, according to Samuel Fairbank, a crystalline principle, *Chimaphilin*. Pipsissewa is nearly equivalent to uva ursi in its therapeutic value, though not so effective. The dose of the fluid extract (EXTRACTUM CHIMAPHILÆ FLUIDUM, U. S.) is a teaspoonful (4 C.c.) three or four times a day.

JUNIPERUS.—*Juniper* is the fruit of the common juniper, Juniperus communis, of Europe and this country. These berries are round, bluish bodies, about the size of a large pea, of a sweetish, terebinthinate, aromatic taste. They owe their properties to a volatile oil (OLEUM JUNIPERI, U. S.). They yield to boiling water and to alcohol. Juniper is gently stimulant and cordial to the stomach. Upon the kidneys the oil exerts a decided stimulant action, and when freely given is capable of irritating the renal organs above the secreting point, and of producing lessened secretion, strangury, and even suppression of urine. Juniper is largely used as an adjuvant to cream of tartar or the alkaline diuretics. On account of its stimulant local influence upon the alimentary canal, it renders the cream of tartar far more acceptable to the stomach, and at the same time aids its diuretic action. Sometimes juniper is employed for its stimulant action on the mucous membrane of the genito-urinary organs in *chronic pyelitis* and in *chronic catarrh of the bladder*. In the form of the compound spirit (SPIRITUS JUNIPERI COMPOSITUS, U. S.), or its equivalent, *gin*, juniper is often useful in the subacute *congestion of the kidneys* frequently seen in old persons, and characterized by aching in the loins and lessened urinary secretion without more serious symptoms. Dose, two to four fluidrachms (7–15 C.c.). The infusion is made by macerating an ounce of the berries in a pint of boiling water for an hour, the whole to be taken in divided doses during twenty-four hours. The

dose of the oil (OLEUM JUNIPERI, U. S.) is from five to fifteen drops (0.3–1 C.c.); of the spirit (SPIRITUS JUNIPERI, U. S.), from thirty to sixty minims (2–4 C.c.).

OLEUM ERIGERONTIS. U. S.—*Erigeron Canadense*, or *Canada Fleabane*, contains a large proportion of a yellowish volatile oil of a rather pleasant odor and taste, which has properties resembling those of turpentine, but much less stimulating. It may be employed in affections of the *genito-urinary organs* and in passive *hemorrhages*. It is especially valuable in *menorrhagia*. According to Starke,[62] it is very efficacious in *gonorrhœa*. The dose is five to twenty drops (0.3–1.2 C.c.) every two or three hours, and is best administered on sugar.

OLEUM SANTALI, U. S., is a pale yellowish, strongly aromatic volatile oil, of a pungent, spicy taste, from the distillation of the wood of Santalum album. It is insoluble in water, but readily soluble in alcohol. When pure, it is a local irritant and probably capable of affecting the general system, although its physiological action has not been properly investigated. S. Rosenberg[63] has noticed after doses of sixty drops a day irritation of the alimentary canal, burning in the urethra during urination, and an eruption of small red prominences upon the entire surface of the body, involving even the conjunctiva. Oil of sandal-wood is very efficient in *chronic bronchitis* and in the advanced stages of *acute bronchitis*, also in *gonorrhœa* after the first period of acute inflammation. From ten to twenty minims (0.6–1.2 C.c.) of it may be given, in capsule or emulsion, three or four times a day.

ZEA. U. S.—The styles and stigmas (the *silk*) of Zea Mays, or Indian corn, has been strongly recommended as a mild stimulant diuretic, which has local anæsthetic influence, and is very useful in *acute* and *chronic cystitis* and in *uric acid* and *phosphatic gravel*. According to Vauthier,[64] its active principle is maizenic acid.* It may be given *ad libitum* in *infusion* (two ounces to the pint of boiling water); the dose of the fluid extract (EXTRACTUM ZEÆ FLUIDUM, U. S.) is one to two teaspoonfuls (4–7 C.c.) every two to three hours; of the maizenic acid, one-eighth of a grain (0.008 Gm.) may be given every two hours.

TEREBINTHINA—TURPENTINE. U.S.

Canada Turpentine (TEREBINTHINA CANADENSIS, U. S.), or *Canada Balsam*, is the product of Abies balsamea, or Balm of Gilead, or American Silver Fir, as it is variously named, a beautiful evergreen indigenous to the extreme Northern United States and to the British provinces. It is a thick and viscid but clear, yellowish liquid, which by age and exposure becomes converted into a hard, brittle, translucent, resinous mass.

* Consult also *Arch. Méd. Belg.*, Aug. 1886; *La France Méd.*, 1880, xxvii. 99; *L'Union Méd.*, April, 1880; *Med. News*, xliii. 372.

Canada Balsam is very rarely, if ever, used in medicine, but resembles turpentine in its action on the system: when fresh it contains about twenty per cent. of the volatile oil, which is its active ingredient.

White Turpentine (TEREBINTHINA—TURPENTINE. U. S.) is the concrete oleoresin obtained by incising Pinus palustris and other species of pine. The supply in the American market comes almost exclusively from North Carolina and other of our Southern States. It is rarely, if ever, itself used in medicine, but by distillation is separated into a volatile oil and a resin (*Rosin*), which is official under the name of RESINA. EMPLASTRUM RESINÆ, U. S., *Adhesive Plaster*, or, in ordinary language, *Sticking Plaster*, is formed by adding rosin to lead plaster. CERATUM RESINÆ, U. S., *Resin Cerate*, or *Basilicon Ointment*, contains rosin, yellow wax, and lard; it is used as a mildly stimulating application to indolent *burns*, *ulcers*, etc.

OLEUM TEREBINTHINÆ—OIL OF TURPENTINE. U.S.

This is a yellowish, highly inflammable oil, of a strong peculiar odor and a hot biting taste, moderately soluble in alcohol, freely so in ether, very slightly so in water. By heating with muriatic acid it is converted into a red liquid and a white crystalline substance, which, from its resemblance to camphor, has received the name of *artificial camphor*. Turpentine is remarkable for having the property of absorbing oxygen and converting it into ozone.*

PHYSIOLOGICAL ACTION.—Turpentine is a powerful irritant, causing in a very short time inflammation in any tissue with which it comes in contact.

When taken by a healthy person in moderate doses, it produces a sense of warmth in the stomach, soon followed by exhilaration, and, if the amount be sufficient, giddiness and even a species of intoxication. The pulse is increased in force and frequency. The turpentine escapes from the body through the lungs and kidneys, imparting its own odor to the breath and that of violets to the urine. Although several recorded instances prove that turpentine is capable of producing death, cases of serious poisoning by it are rare, and a lethal result is exceedingly so. The symptoms noted in poisoning by it are most of them constant, but vomiting and purging are present in some cases and not in others. Unconsciousness is generally complete, and occasionally is accompanied by dilated pupils; the urine is very much lessened in quantity, often bloody, not rarely suppressed; the skin is sometimes dry, sometimes moist; the pulse is feeble, rapid, and generally regular.

The lethal dose must be very large, but it is not definitely known, since recovery from four ounces in an infant fourteen months old has been reported. In Maund's[65] case, death was supposed to have been

* For a study of the effect of the ozonizing turpentine oils, see Pallop (*Dorpat Thesis*, 1889).

produced in an intemperate woman by six ounces; and Philip Miall[66] has recorded an instance of death caused in an infant fourteen weeks old by turpentine, of which half an ounce was thought to have been taken.

Our knowledge of the action of turpentine upon the circulation is very imperfect: the results which have been obtained by experimenters are so diverse as to indicate that different varieties of the oil affect the circulation differently, or else that the oil alters in its physiological influence when allowed to stand and absorb ozone. R. Kobert,[67] using the European turpentine, found that in moderate doses it exerted a powerful stimulating influence upon the inhibitory reflex centre, and also elevated the blood-pressure by stimulating the vaso-motor centres. Very large doses appeared to paralyze both of the centres spoken of, causing decided fall in the arterial pressure. The respiration was first increased in frequency, but later very much diminished. The blood became very dark, and the heart was finally paralyzed. The vagi and depressor nerves did not appear to be affected, nor indeed did any of the peripheral nerves or the muscles. It is said that these results are in accord with those previously published by Azary in the Hungarian language, and Hoppe[68] concludes as the result of his own experiments, presumably made with European oil of turpentine, that the vaso-motor nerves are very early influenced by the drug. On the other hand, in a series of experiments made in the laboratory of the University of Pennsylvania by H. A. Hare[69] with American oil of turpentine, it was found impossible to raise the arterial pressure for more than two or three minutes, and then no more than ten millimetres of mercury. Large doses produced a pronounced fall of arterial pressure, with great cardiac depression, to which, indeed, Hare attributes the fall of the blood-pressure. Doses which had no effect on the blood-pressure increased the frequency of the pulse for a length of time. The increase of the pulse-rate was evidently due to an action upon the heart itself, for it occurred when the turpentine was applied directly to the heart of the frog as well as in the dog after section of the accelerator nerves and the vagi. When large doses were administered the pulse became slow,—probably, as Hare believes, as the result of stimulation of the pneumogastric nerves, since section of these nerves was followed by the normal rise in pulse-frequency. Léon Crucis[70] has made some experiments which indicate that when turpentine is given in toxic doses to rabbits it increases the coagulability of the blood and gives rise to numerous minute hepatic and pulmonic thrombi.

F. Fleischmann[71] found that two drops produced paralysis in the frog,—first of voluntary and afterwards of reflex activity; in the cat and in the rabbit, toxic doses abolished reflex activity, but caused violent lethal convulsions. The preservation of voluntary movement in the frog after the loss of reflex activity, which has been confirmed by Hare, indicates that toxic doses of turpentine paralyze the sensory nervous system, either in the cord or in the peripheral nerves.

The irritant action of turpentine upon the kidneys and genito-urinary tract is very decided. When moderate doses (ten drops every three hours) of turpentine are taken, there are usually no renal symptoms produced, except a slight increase of the urine. Somewhat larger amounts, when exhibited, are apt to give rise to aching in the loins and to frequent micturition, with perhaps urethral pain accompanying the act. If still larger quantities are ingested, these symptoms are intensified, and at the same time the secretion of urine is diminished. After very large repeated doses of the drug, the aching in the loins is very great, often with spasmodic pain in the ureters ; a constant desire to pass water struggles with the inability to micturate, caused by the urethral spasm ; the urine is very scanty, albuminous, and even bloody ; priapism may be present, and an intolerable irritation may affect all the pelvic organs.

THERAPEUTICS.—Externally the oil of turpentine is very much employed as a powerful counter-irritant. It is useful more especially when it is desired to act upon a large extent of surface. When a very intense permanent local impression is required, a blister is to be preferred. Thus, in *pleurisy* a blister may be used, in *bronchitis* turpentine stupes. In preparing the latter the turpentine should first be warmed by setting the vessel containing it in hot water, then a piece of flannel, just previously saturated with hot water and wrung out as dry as possible, should be dipped in the turpentine and again wrung out. It is then ready for application, and may be left on from fifteen minutes to half an hour, according to the sensitiveness of the skin.

Another local use of the oil of turpentine is as an addition to enemata. From a teaspoonful to a tablespoonful of it mixed with double its amount of olive oil renders opening enemata much more active, especially in causing the expulsion of flatus. Turpentine enemata containing much of the oil in a small bulk are also constantly used with good effect in arousing the system from stupor arising from narcotic poison or similar causes.

In *ulceration of the bowels* turpentine taken by the stomach is often very efficient, probably acting locally in the intestine, and in old gastric ulcers good results are sometimes derived from its use. In a single large dose (half to one fluidounce, with an equal amount of castor oil) it is an efficient vermifuge. It may also be used as a stimulant in *low fevers*, particularly when the tongue is dry and red.

In *typhoid* or *enteric fever* it without doubt acts as a local stimulant to the ulcerated bowel, besides influencing the general condition of the system. There are two conditions or stages in the diseases named in which it is especially useful,—indeed, is of incalculable service. About the end of the second week the tongue sometimes becomes very dry, red, chapped, perhaps coated in the centre with a brownish fur, and at the same time marked meteorism develops. Ten drops (0.6 C.c.) of turpentine every two hours during the day and every three hours during

the night will in the majority of cases remove the bad symptoms noted. That the action of the oil is largely a local one is shown not only by the arguments of the introducer of the practice, George B. Wood, but also by the value of the same treatment when diarrhœa persists after the acute stage of the fever has passed. When convalescence is protracted, when there is a constant tendency to the recurrence of diarrhœa,—when, in other words, the ulcers of Peyer's patches are slow to heal,—turpentine acts almost as a specific. These clinical results have received scientific confirmation in the work of Theo. Omelchenko,[72] who finds that the bacillus of typhoid fever will not develop in air containing diluted vapor of turpentine, and dies when the atmosphere is saturated with the vapor. Thymol appears to be even more active than is turpentine.

In *typhoid bronchitis* and *pneumonia*, especially as intercurrent in typhus fever and similar diseases, turpentine applied externally and taken internally is often very useful. The same may be said of the low forms of *puerperal fever*. In this disease the abdomen should be kept covered with fomentations of the oil and of warm water alternately, the counter-irritant being used as constantly as a proper regard for the skin of the patient will allow. Internally it should be given in very large doses (ten to fifteen minims every two hours).

In *hemorrhages* from the stomach, bowels, or lungs turpentine has acquired celebrity, but it is hardly so much used as formerly. It is in the ataxic cases that it is useful. We have very rarely employed it, as the *oil of erigeron* has seemed even more efficacious, and is much more pleasant to the patient. In *purpura hæmorrhagica* turpentine has been highly praised.

Oil of turpentine is never employed to increase the flow of urine for the purpose of affecting serous effusions. As a diuretic, it is used solely for its local influence upon the organs. *Excessive diuresis* sometimes is apparently dependent upon a relaxed condition of the kidneys, and under these circumstances oil of turpentine may be of service. *Chronic pyelitis*, *chronic cystitis*, and *gleet* may be benefited by its use.

In giving turpentine in these cases, it should always be borne in mind that, with the exception of cantharides, it is the most actively stimulating of all the diuretics, and must be employed only when such a remedy is called for. In those comparatively rare cases of *urinary incontinence* which are dependent upon debility of the bladder, turpentine is sometimes of great service. When the same symptom is spasmodic, the remedy, of course, is harmful. In absolutely passive *hæmaturia*, in *impotence*, in certain conditions of *spermatorrhœa*, and in *amenorrhœa*, when great local debility exists, turpentine may be tried with fair hopes of its being useful.

ADMINISTRATION.—The dose of turpentine is ten to fifteen drops (0.6–0.9 C.c.) in emulsion, given from four to six times a day. If glycerin and oil of peppermint be added to the emulsion in such proportion that half a teaspoonful of the one and one or two drops of the other are

taken with each dose, they will almost completely disguise the taste of the remedy. The drop of turpentine is about equal to half a minim.

It has been asserted that oil of turpentine is a powerful bactericide; but the experiments of Koch and of Christmas-Dirckinck-Holmfeld [73] appear to show that its general antiseptic properties are feeble.

COPAIBA—COPAIBA. U.S.

The oleoresin of Copaiba Langsdorffii and of other species of Copaiba, large trees growing in Brazil. Copaiba is a yellowish liquid, of varying viscidity according to age, of a strong, terebinthinate, peculiar odor, and a bitter, burning, disagreeable taste. It mixes uniformly with absolute alcohol and volatile and fatty oils, and is readily dissolved by ether. It contains a volatile oil, a small quantity of soft, viscid resin, about fifty per cent. of a hard, acid resin, and a peculiar crystallizable acid, *copaivic acid*, which, according to Bernatzik, is unimportant, the activity of the drug depending upon the oleoresin.

Physiological Action.—The local action of copaiba is that of an active stimulant or a mild irritant. When taken internally, it yields its active principle to absorption and elimination through the kidneys. The elimination takes place slowly, as Bernatzik [74] found the oil in the urine as much as four days after its ingestion.

Upon the general system copaiba has little influence; eighteen grammes of its volatile oil, taken in three doses during twelve hours, caused only a slight elevation of the pulse-rate and of the temperature, with later vomiting and purging, and still later burning in the urethra and strangury (Bernatzik). In susceptible persons the evidences of the local action of the drug are more marked, it causing decided symptoms of gastro-intestinal irritation, accompanied by marked fever and irritation of the urinary organs, such as strangury, and even almost complete suppression. In Bernatzik's trials fifteen grammes of the resin, taken within five hours, produced violent purging and vomiting, with much abdominal pain.

The discovery in 1841 by G. O. Rey, that the addition of nitric acid to the urine of persons taking copaiba will produce a precipitate resembling that of albumin, has led to much discussion. To obtain this precipitate the copaiba must be freely given. As shown by Bernatzik, the precipitate probably consists of the oxidized oil united to some urinary principles. The *copaiba-red* of Quincke is a substance found in the urine of persons taking the oil of copaiba; it is an acid, whose salts have the property of reducing the oxide of copper and of polarizing to the left, and may be a source of error in the diagnosis of diabetes. When a pure copaiba resin is used, although the copaiba-red cannot be detected in the urine, the urine still responds to Trommer's test for sugar.

As a stimulant to the genito-urinary mucous membrane, copaiba is distinctly more active than buchu, but less irritating than the oil of tur-

pentine. It may be used in chronic *pyelitis* and *cystitis*, but is chiefly employed in advanced stages of *gonorrhœa;* if administered during the height of the inflammation in these diseases, it is liable to aggravate the symptoms. It is also capable of affecting other mucous membranes than that of the genito-urinary tract, so that it may sometimes be given with advantage in old indolent *ulcers* of the stomach, in *chronic diarrhœa* and *dysentery*, in *advanced bronchitis*, and especially when in *chronic bronchitis* there is very free muco-purulent expectoration. As a local application it is sometimes very advantageous in *chronic chilblains* and other diseases of the skin. In doses of forty-five grains (3 Gm.) a day the resin is said to be actively hydragogue and effective in *dropsies* which are not dependent upon renal disease. Dose of copaiba, half to one fluidrachm (2–4 C.c.), in capsules; of the oil (OLEUM COPAIBÆ, U. S.), which is isomeric with oil of turpentine, eight to fifteen minims (0.5–1 C.c.), in capsules. MASSA COPAIBÆ, U. S., is an entirely ineligible preparation.

CUBEBA—CUBEB. U. S.

The unripe fruit of Piper cubeba, a climbing plant of Java and other portions of the East Indies. These berries are blackish-veined, about the size of a small pea, and have attached to them a short stalk three or four lines long. Their odor is aromatic and peculiar; their taste warm, camphoraceous, and peculiar. They contain *cubebic acid*, *cubebin*, volatile oil, and resin, and are fully represented by the official oleoresin. Bernatzik[75] has found that cubebin is inert, which is in accord with the statement of Heffter,[76] that cubebin passes through the alimentary canal without absorption, so that it is possible to recover from the fæces almost the whole amount ingested.

Cubeb is a local stimulant which has very little effect upon the general system. In large doses it produces a gastric and genito-urinary irritation proportionate in severity to the amount taken. Like copaiba, it occasionally causes an urticaria, which is probably due to the gastric irritation. It yields to absorption and elimination its active principles, which can be detected in the urine by the addition of nitric acid, when a precipitate resembling that of albumin occurs.

In Bernatzik's experiments ten grammes of magnesium cubebate caused slight acceleration of the pulse and gastric uneasiness, with increased elimination of uric acid. Half an ounce of the oil, taken in thirty-six hours, produced very decided gastric irritation, with the appearance in the urine of the oxidized oil in the form of a resin, and a very great decrease in the elimination of uric acid. After fifty grammes of the powdered cubeb the gastro-intestinal irritation was most pronounced and the nitric acid precipitate in the urine very abundant.

Cubeb is used to relieve precisely the same conditions as is copaiba. In many cases the best results are to be obtained by the combined employment of the two remedies. It has received much praise as an internal remedy in chronic *hemorrhoids*. It is useful as a local stimulant in the relaxation

of the larynx frequently seen in public speakers following slight colds and over-use of the voice, chewing the berries often bringing relief to the throat and tone to the voice. The powdered drug may be used as a snuff in *coryza*. In this disease, as in all others, cubeb should not be employed in the earlier stages before secretion has been established, but later in the affection when the discharge is profuse.

The dose of the powdered cubeb is from half to three drachms (2–11 Gm.); of the volatile oil (OLEUM CUBEBÆ, U. S.), fifteen drops (1 C.c.), given in capsules and gradually increased to half a drachm, unless some effect is previously produced upon the urinary organs; of the fluid extract (EXTRACTUM CUBEBÆ FLUIDUM, U. S.), ten to forty minims (0.6–2.5 C.c.). The best preparation is the oleoresin (OLEORESINA CUBEBÆ, U. S.), dose, ten to fifteen minims (0.6–1 C.c.), in capsules, increased as required.

MATICO. U. S.—*Matico*, the dried tops of the Piper angustifolium of Peru, contains a volatile oil, resin, and, it is said, a bitter principle, *maticin*. It is a softish mass which is largely employed as a styptic, and probably acts chiefly mechanically, coagulating the blood in its interstices, adhering to the wound, and thus arresting the hemorrhage. It has also been employed in internal *hemorrhages* and in *gonorrhœa*. In these affections it probably acts similarly to oil of turpentine, although much less of a stimulant and much more feeble. The fluid extract (EXTRACTUM MATICO FLUIDUM, U. S.) and the tincture (TINCTURA MATICO —ten per cent., U. S.) may be respectively given in doses of forty-five minims (3 C.c.) and two fluidrachms (7 C.c.).

KAVA.—The root of Piper methysticum is used in the Sandwich Islands as the basis of an intoxicating liquor known as kava-kava, kawa, or ava. It contains a crystalline principle analogous to piperin, which its discoverer, Gobley, called *methysticin*, besides an acrid resin, for which the name of *kavin* has been proposed, and a volatile oil.

L. Lewin[77] finds that when the kava resin is injected into the frog it produces a very pronounced loss of sensation at the point of injection, due to a paralysis of the peripheral endings of the sensory nerves, and that after the absorption of the remedy there is loss of voluntary motion and reflex activity, which is chiefly of spinal origin. In experiments made upon the warm-blooded animals he obtained similar phenomena,—namely, local anæsthesia at the point of injection, followed, after absorption, by general paralysis, due to a direct depression of the motor side of the spinal cord, the motor nerves and the muscles remaining intact. According to Dario Baldi,[78] the active principle of kava produces in the dog a very short period of excitement of the sensory nerves, followed by a complete paralysis, at a time when the whole motor system still responds to stimuli.

In small doses kava is said to act as a stimulant tonic, but when taken in large amounts to produce an intoxication which differs from that caused by alcohol in being silent, drowsy, and without emotional exaltation.

The great loss of muscular power which is said to follow kava debauch in those unaccustomed to the use of the drug shows that its influence upon the spinal centres in man is the same as in other mammals. According to Baldi, Randolph, and Lewin, the resin of kava is a local anæsthetic of extraordinary persistency of action, but it appears to be too irritant for practical use. A decoction of the root is used in Oceanica very largely in the treatment of *gonorrhœa*, and its value has been strongly affirmed by Sanné.[79] The dose of the root itself, given in *decoction*, is half a drachm three or four times a day; of a *fluid extract*, half a fluidrachm (2 C.c.).

CANTHARIS.—*Cantharides* is considered elsewhere in detail (see EPISPASTICS), and it is only necessary here to say a few words in regard to its use in diseases of the genito-urinary tract. The active principle of Spanish flies is certainly eliminated by the kidneys, and acts therefore locally upon these organs, as well as upon those over which their secretion flows. The influence exerted by this means is simply one of intense irritation, cantharides being an irritant to these organs in any dose sufficiently large to have an effect. Indeed, of all the official drugs cantharides is the most actively irritant to the kidneys and their subordinate organs. Consequently it is employed only when an intensely stimulant action is desired, as in obstinate *gleet*, in which affection it is often combined very advantageously with the tincture of ferric chloride. In *pyelitis* and *cystitis* it is very rarely indicated, but may be cautiously used in very chronic cases. The *tincture* of cantharides is the only preparation used internally. (See EPISPASTICS.)

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FAMILY V.—DIAPHORETICS.

DIAPHORETICS are those medicines which are employed to increase the action of the skin. It is scarcely in place here to discuss the results of suppression of the functional activity of the skin or the importance of the surface-elimination to the system. It does seem well, however, to call attention to the fact that the perspiratory glands have a double function to perform,—that of elimination, already alluded to, and that of keeping down the temperature of the body during exposure to heat. When a man enters a Turkish bath the temperature of which is perhaps 160° F., or when he works in the sun on a very hot day, there is, if he be used to such exposure, little or no rise in the temperature of the body, because the surface-glands secrete sweat so actively as to expose a great amount for evaporation, and by the conversion of so much water into vapor such an amount of heat is absorbed—*i.e.*, converted from heat into repulsive force—that the body is cooled. The reason that even a moderate degree of heat in a moist atmosphere is intolerable is because evaporation cannot take place.

From what has already been stated, it is obvious that the use of dry external heat, or rather exposure to a hot atmosphere, is a powerful means of producing perspiration. It may be applied either in the form of the *Turkish bath*, in which the air of the hot chamber is very dry, or in the *Russian* or *vapor-bath*,* in which the atmosphere is surcharged with hot vapor. Neither of these baths has any other physiological property than that of a sweat-producer.

Hot-water baths offer another very successful method of inducing profuse perspiration. The patient should be placed in a bath of about 100° F., and remain there from fifteen to twenty minutes, during which time, by the repeated addition of very hot water, the temperature should be raised to 110° F., or to such point as the patient can endure. Warmed blankets having been plentifully provided, the sick man should be lifted from the bath into them, be closely wrapped up, and so left for

* For home use there are in the market various "Cabinet Baths," so called, which afford a cheap and efficient means of giving vapor-baths. The term Turkish bath is here applied to the bath used in this country under that name. This bath appears not to be a copy of the Oriental bath, but merely a derivative from it. Writers affirm that in the East the sudarium, or sweating-chamber, rarely has a temperature of more than 98° F.; in London we have been in a Turkish bath at 200° F.; from 140° to 160° F. is a common temperature in American baths.

three or four hours before being transferred to the usual bed. According to A. Steffen,[1] after this use of the bath the body has been proved to undergo loss of weight continuously for one or two days.

The popular belief that after a sweat there is a greater liability than usual to take cold appears to us to be well founded : care must, therefore, be exercised to avoid exposure after the hot bath of any kind. The liability to take cold may, however, be overcome by the use of the cold douche or plunge-bath.

The possibilities of the hot-water bath as a therapeutic measure are probably much greater than is ordinarily recognized. In severe *burns*, in *nervous shock*, and in various skin diseases continuous immersion would probably often be found of the greatest service. According to Baelz,[2] the baths which are habitually taken by the entire native population of Japan are at a very high temperature (109° to 114° F.), and the immersion continuous during the whole evening. The mouth temperature rises to 104° or 105° F., whilst the pulse becomes very full and increased in frequency, with marked evidences of relaxation of the arteries. When there is a high grade of atheroma, the softening of the arteries after an hour's bath is very pronounced. Baelz believes that there is no increase in the elimination of nitrogenous matter, and that the Japanese custom is extremely useful, because, the winter being cold and the houses not heated, the people lose bodily heat during the day, and for two pennies in the evening acquire a supply of heat which lasts through the night.

Profuse sweating is always more or less exhausting, but is not nearly so much so as purging, and therefore may be practised in dropsical patients too feeble to allow of the use of purgatives. The hot baths are not, however, altogether free from danger or objection. Sometimes in the Turkish and Russian baths the patient fails to sweat freely, and a feeling of distress, a bounding, rapid pulse, and perhaps severe headache develop themselves : under these circumstances the bodily temperature rises, and a fever develops, which may go on to the production of a true "thermic fever," and perhaps terminate in sudden death. This is an exceedingly rare result, and one that can never occur if the patient is removed from the hot chamber so soon as any unpleasant symptoms are manifested. Sudden death has been recorded once from "sunstroke" in a patient while taking the "Turkish bath," also once from "congestion of the lungs."[3]

The use of hot baths of any kind is, of course, contra-indicated by the existence of fever ; but, according to Steffen, the hot-water baths are pre-eminently contra-indicated by the existence of congestion or œdema of the lungs, or of a tendency towards these disorders, since under such circumstances the bath greatly increases the disease, or precipitates a perhaps fatal attack. Our own experience corroborates these statements. We have seen, under the conditions mentioned, the most frightful dyspnœa result from the use of the hot-water bath. If disturbance of the respiration comes on during the bath, the patient should immedi-

[illegible] be taken out, and, if the symptoms be urgent, cold water should be freely dashed over the head, neck, and chest. Severe cardiac disease is also a contra-indication both to the Turkish and Russian or vapor-bath.

Precisely as water may act as a diuretic by increasing the fluidity and amount of blood, so may it also act as a diaphoretic, provided that it is directed to the skin by being itself given warm and aided by the use of external heat; hence the importance of hot drinks when it is desired to produce free sweating. The colliquative so-called "night-sweats" of phthisis are undoubtedly largely due to a paralytic weakening of the blood-vessels of the skin. In similar manner aconite, veratrum viride, tartar emetic, and other substances which profoundly affect the vaso-motor system produce a free sweating which resembles that often seen in collapse from other than drug causes.

Diaphoretics are employed in the practice of medicine to fulfil the following indications:

First. *To arrest forming diseases* of not very severe type, probably by causing a flow of blood to the surface, and thereby relieving slight internal congestions, and possibly by eliminating principles which have been retained in the blood instead of being excreted as they ought to have been. In *general cold*, in *muscular rheumatism*, in *suppressed menstruation*, and other results of exposure to cold and of checked perspiration, the diaphoretics afford the most efficient means at our command for restoring the normal functions.

Second. *To favor absorption.* In *dropsy* the diaphoretics are of very great value, often aiding diuretics and purgatives in effecting a cure, and sometimes, when these fail, or when circumstances forbid their use, rescuing the patient from impending death. None of the medicinal diaphoretics except jaborandi is of sufficient power to be relied upon in dropsy. The Turkish, the Russian, and the hot-water bath are capable of producing sufficient sweating to cause absorption of dropsical fluid, but must be vigorously employed.

Third. *To aid in the subsidence of diseases* which naturally pass off with a sweat. The chief use of diaphoretics for this purpose is in *miasmatic fevers*, especially in the *remittent* form of the affection, when the sweating stage fails to develop itself thoroughly and the paroxysms run into one another. Even in the single paroxysm of *intermittent fever*, by hastening the closing stage, diaphoretics will often shorten the paroxysm.

Fourth. *To eliminate noxious materials* from the blood. The old humoral idea that the groundwork of such diseases as fevers is a distinct *materies morbi* which can be eliminated from the blood has no sufficient demonstration to be accepted, and, although diaphoretics do good in *fevers*, yet it cannot be granted that it is in this manner. The very great power of increased diaphoresis in cooling the body through surface-evaporation has already been dwelt upon, and much of the good effected by diaphoretics in diseases of high temperature probably has its origin in this power.

Modern science seems clearly to point out that diaphoretics may aid in separating from the blood retained secretions, and may to some extent replace the action of the kidneys when these organs are disabled by disease.

In 1851 Schottin[4] discovered urea in the sweat of patients suffering from the collapse of cholera. Not only has the discovery of Schottin been confirmed by the researches of G. O. Rees,[5] of Fiedler,[6] of Hirschsprung,[7] of Kaup and Jürgensen,[8] of Leube,[9] and of G. Deininger,[10] but it has also been abundantly proved that the skin excretes urea freely during the advanced stages of Bright's disease, and also during the partial urinary suppression of scarlatinal desquamative nephritis. The urea in renal disease may even form a distinct crystalline powder on the skin, but it is most abundant about the mouths of the sweat-glands. We believe Landerer was the first to announce that urea is present in the sweat of healthy persons; and, although excellent chemists have been unable to detect it, its presence at times can no longer be denied, since it has been found not only by Landerer, but also by Funke[11] in 1858, by Meissner,[12] and by Leube; Fourcroy (quoted by Rees) has also found it in the sweat of horses. By a series of elaborate experiments, Leube has rendered it probable, if he has not actually proved, that in health there is such a relation between the skin and the kidneys that when the former is very active the latter excrete less than the normal amount of urea.

When to the facts already cited are added the observation of Griesinger, that in diabetes the perspiration contains sugar, and the well-known circumstances that in rheumatism the sweat contains lactic acid, and in jaundice biliary products, the value of diaphoretics as a means of getting rid of retained excretions becomes manifest. For this reason, in *Bright's disease*, especially of the acute form, they are of the greatest value, acting beneficially in three different ways,—by drawing the blood to the surface, and thereby relieving any internal congestions of the kidneys or other organs that may exist; by promoting the absorption of dropsical effusions; and by eliminating retained secretions.

PILOCARPUS. U.S.—JABORANDI.

This drug, which has long been employed by the natives of South America, received its first notice, under the various names of *Jaborandi*, *Jaguarandy*, and *Jamguarandi*, from T. J. H. Langgaard in his *Diccionario de Medecina domestica*, Rio Janeiro, 1865. It attracted no attention, however, until 1874, when it was brought to Paris by Coutinho. The leaves* alone are official; of them there are in commerce two varieties: the Rio Janeiro Jaborandi, which is believed to be the product of Pilocarpus selloanus, and the Pernambuco Jaborandi, the product of P. jaborandi. The two varieties agree in that the leaves are oval, oblong, and entire, four to six inches long and one and a half to two inches wide, with a bitter taste and a hay-like odor: they differ in that the Rio Janeiro leaves have a tendency to become obovate

* Under the name of Jaborandi various drugs other than the product of Pilocarpus are sold in Brazil. As the Pilocarpus pinnatus has been found to be active when grown in France, it is probable that the Jaborandi plant might be successfully cultivated in our Southern States. Frerichs (*Berlin. Klin. Wochenschrift*, 1875) found the wood inert.

its normal proportion, the amount eliminated in the sweating being estimated at from ten to fifteen grains. Hardy and Ball [14] believed that in their experiments the average amount of urea eliminated by the skin was seventeen grains.

Jaborandi appears to have an extraordinary influence upon secreting glands, not only in the skin but almost throughout the whole body. The nasal mucus is often greatly increased. The assertion of Pilicier,[15] that in a dog with a gastric fistula the gastric juices were greatly increased by the drug, is in conformity with the free vomiting of large quantities of glairy secretion which it causes in man. Morat [16] has noted a temporary increase of the sugar in the blood, an evidence that the glycogenic function of the liver is stimulated. The suprarenal capsules appear to share the action of the drug, since Auguste Pettit [17] has noticed that in animals poisoned by jaborandi there is marked congestion and swelling of these bodies. On account of the antagonism between the skin and the kidneys the diaphoretic dose of pilocarpine may cause a decrease in the urinary flow, but the assertion of Gubler that the alkaloid administered in very small repeated doses has a marked diuretic influence has received clinical confirmation.* According to Gottlieb,[18] pilocarpine causes an increase of both the watery and solid constituents of the pancreatic secretion.

There appears to be some relation between the flow of saliva and that of perspiration produced by jaborandi: if the one is very profuse the other is often, but not always, correspondingly scanty. Sometimes the salivation almost replaces the sweating (Féréol [19]); very frequently it commences before the sweating, and often it is more persistent. During it the mouth is warm, and there is often a feeling of tenseness about the maxillary glands. The saliva contains an abundance of salts and of ptyalin, as well as a small excess of urea. Pilicier, it is true, states that the proportion of albuminous compounds, and especially of *potassium sulphocyanide*, is much diminished, but in Robin's analyses the proportion was even beyond the normal, and Ch. Bougarel has by careful experimentation shown that the power of jaborandi-saliva in converting starch into sugar is equal to that of the normal secretion. According to J. N. Langley, in the frog the mouth and skin, after the exhibition of jaborandi, become covered with a viscid secretion; in the dog, the rabbit, and the cat there is profuse salivation.

* Much interest attaches to the effect of jaborandi upon urea-elimination, but it cannot be considered as determined, except that in various diseases the combined renal and dermal elimination is greatly increased by the drug. Hardy and Ball state that in health urea-elimination from the kidneys is diminished by the drug, while Tyson and Bruen have found it increased both in health and in disease. The experiments have, however, been too few, and especially the conditions of their performance too lax, for much importance to be attached to them. As the result of experiments upon the lower animals, J. Horbaczewski (*Therap. Gaz.*, 1893) believes that there is a distinct relation between the elimination of uric acid and the number of leucocytes in the blood, and that pilocarpine in proper dose increases the size of the spleen and increases also the number of leucocytes in the blood and the quantity of uric acid eliminated.

The action of pilocarpine in increasing secretion is direct and upon the glands themselves. The salivary glands are affected equally before and after section of all of the salivary nerves (Langley[20] and Carville,[21] confirmed by Schwann[22]); also when the drug is injected directly into the gland and prevented from entering the general circulation (Langley). According to the elaborate experiments of Langley upon cats poisoned with pilocarpine, stimulation of the chorda tympani or of the sympathetic nerve causes respectively some increase or lessening of the secretion, but this increase or lessening is not nearly equal to that which occurs in the normal animal, and is due to the action of the nerves upon the circulation, and not to any influence on their secretory fibres. Very large doses of the drug injected into the gland immediately arrest the secretion, and doses of less size given in the same way, while increasing secretion, paralyze both chorda tympani and sympathetic nerve, so that stimulation of them has no effect. It is probable from the last fact that jaborandi has an action upon the secretory gland-cells.

Although the evidence just deduced indicates that an influence is exerted by jaborandi upon the gland-cells, the fact that atropine arrests the jaborandi salivary secretion prevents us from considering it entirely settled that the drug does so act upon the salivary gland-cells rather than upon the peripheral nerve-endings, since there is reason for believing that atropine acts upon the nerve-endings. Fuchsinger (confirmed by Nawrocki) has found that section of the nerves of the cat's leg did not prevent the paws from sweating when jaborandi was exhibited. This demonstrates that the action of the drug is peripheral, not centric. Five or six days after the section, when the peripheral nerve-endings had undergone degeneration, Fuchsinger found that jaborandi was unable to excite sweating. This, however, can hardly be considered to prove absolutely, as Fuchsinger[23] asserts, that the drug acts upon the peripheral nerve-endings and not directly upon the glandular cells themselves, since it is probable that these glandular cells shared the anatomical changes of the nerve-endings.

Jaborandi appears to stimulate the nutrition of the hair, and Prentiss,[24] of Washington, has reported several cases in which the continued internal use of pilocarpine caused the hair to become exceedingly coarse and to change its color from light to dark. H. Rasori[25] has noticed a tuberculated eruption apparently produced by jaborandi. M. Grocco[26] has found that pilocarpine hypodermically injected or locally applied sensibly affects hysterical anæsthesia.

Temperature.—Robin affirms that before and during the early stages of the sweating from jaborandi the temperature rises 1° to 2° F., but afterwards falls as much below the normal point and remains depressed for one or two days. This primary rise of temperature has been noted by other observers,* but is frequently absent altogether or very trifling.†

* See Ringer (*Lancet*, 1873, i. 157), Greene (*Phila. Med. Times*, vi. 56), Scotti (*Berlin. Klin. Wochens.*, 1877, 141), Pilicier (*Med. Centralbl.*, 1876, 429), and Weber (*Ibid.*, 770). Pilicier noted that the rise occurred in the axilla, but not in the rectum: this would indicate that it is a local phenomenon, the result of a heating of the *surface*, not of the interior, of the body.

† Consult Riegel (*Berlin. Klin. Wochens.*, 1875, 86), Bardenhewer (*Ibid.*, 1877, 8), and Auschmann (*Ibid.*, 353).

The subsequent fall of temperature, which is a constant phenomenon, probably depends in great part, or altogether, upon the loss of heat during the sweating.

Circulation.—The action of jaborandi upon the circulation has been studied by Langley,[27] E. Leyden,[28] Kahler and Sayka,[29] and Harnack and Meyer.[30] The phenomena noted by these observers are in most respects in accord, but Kahler and Sayka using the extract of jaborandi, and E. Leyden commercial pilocarpine, have found the pulse either as a constant or occasional phenomenon at first increased in its rate, while Harnack[31] has never seen this with chemically pure pilocarpine. It has been shown, however, by E. T. Reichert[32] that the result reached by Harnack was not due to the purity of the alkaloid, but to his not having used sufficiently minute doses. According to Reichert's experiments, the minute dose increases, the large dose decreases, the pulse-rate, there being a broad line between the two effects in which the pulse is normal. Immediately after the injection of the alkaloid into the jugular vein the arterial pressure falls, but in a few moments the characteristic phenomena of a slow pulse with increased arterial pressure come on. This slowing of the pulse is not prevented by previous section of the pneumogastric, but is at once set aside by an injection of atropine (Langley, Leyden, Harnack and Meyer), as is also the diastolic arrest of the heart which pilocarpine produces in the frog. Harnack and Meyer therefore believe that in both the frog and the mammal the chief cardiac influence of the alkaloid is exerted upon the intra-cardiac inhibitory ganglia; but Ringer[33] finds that jaborandi and atropine act antagonistically upon the ventricles separated from the auricles, and, as the ventricles contain no inhibitory ganglia, some other explanation of the antagonism must be found.* The rise of the arterial pressure is stated by Harnack and Meyer to be prevented by the use of curare and artificial respiration, and to be, therefore, a secondary, not a direct, result of the drug's action: it is probably due to the convulsive muscular contractions produced by the drug. In the latter stage of the poisoning the arterial pressure falls. As in the experiments of Harnack and Meyer asphyxia in this stage did not cause rise of pressure, although the heart appeared still to retain its force, the vaso-motor system is probably paralyzed, a conclusion confirmed by the later experiments of Reichert. The pulse still continues slow, although, according to Harnack, the vagi are completely paralyzed.

Respiration.—According to the experiments of Morat and Doyon,[34] pilocarpine produces a distinct slowness of the respiration, and as a respiratory poison is the antagonist to atropine.†

* Ringer's explanation seems at present the most probable. It is, that pilocarpine paralyzes the heart by combining with the molecules of the excito-motor apparatus and of the muscular tissue, and that atropine displaces the pilocarpine and thereby substitutes its own action.

† H. Dreser (*Arch. f. Exper. Path. u. Pharm.*, 1892, xxx.) has experimentally found that pilocarpine markedly increases the oxygen in the air of the swimming bladder of the carp.

Sexual Organs.—Jaborandi does not appear to have any power over the sexual organs, except the pregnant womb. Cases of abortion during its use have been reported by Masmann (quoted by Larvand [35]) and by Schanta,[36] but in the hands of other observers the drug has appeared to have little, if any, abortifacient influence, and Hyernaux and Chanteril have found it powerless in the lower animals (quoted by Larvand). When, however, the pregnant female is at her full term, the drug may affect the uterine contractions, as Larvand and others have noted an increase of the pains, or even a precipitation of labor, both in women and in the lower animals. Nevertheless, the oxytocic powers of jaborandi are very feeble.*

Motor System.—In man, muscular tremblings have been observed during the action of jaborandi, but it is doubtful whether they are due to a direct action of the remedy. In the frog, as first noticed by Murrell,[37] small doses (three milligrammes of pilocarpine) produce violent convulsions with heightened reflex activity, while larger amounts cause complete palsy. According to Harnack and Meyer, the convulsions are due to spinal stimulation, and the paralysis partly to overwhelming of the spinal centres and partly to paralysis of the muscles, the motor nerves themselves not being affected. The action of the drug upon the musculo-nervous system is entirely subservient to its other effects.

Eye.—When applied to the eye, pilocarpine produces contraction of the pupil, tension of the accommodative apparatus, and an approximation of the near and far points of distinct vision.† Tweedy also states that there is impairment of vision, due to benumbing of the retina. According to P. Albertoni, the myosis is followed by a moderate but persistent mydriasis, and is not prevented by previous section of the oculo-motor nerve or of the upper cervical sympathetic ganglion. It is certainly the result of a peripheral influence. Galezowski, who uses a solution of one part of a pilocarpine salt in fifty parts of water, affirms that it answers as well as a solution of eserine in diseases of the eye, and has the great advantage of not producing irritation.

THERAPEUTICS.—Jaborandi is by far the most reliable and powerful remedy of its class, and is always selected when it is desired to produce a very active sweating, as in *uræmia* or in *dropsy*. Both in *acute* and *chronic Bright's disease* it is of very great value, either as an aid to or as a succedaneum for the vapor-baths. The sweating should be repeated at regular intervals, varying from one a day to one a week, according to the nature of the case.

Not only is jaborandi valuable for the removal of distinctly excrementitious material from the blood, but it is often of the greatest service in arresting the development of a forming disease, probably by eliminating peccant matters. Thus, in the onset of an attack of *influenza*, in the be-

* See *British Medical Journal*, 1879, ii. 509; also *Wien. Med. Blatt*, 1879, ii. 1178, 1207.

† See John Tweedy (*Lancet*, 1875, i. 159), C. Scotti (*Berl. Klin. Wochens.*, 1877, 143), and Galezowski (*Med. Times and Gaz.*, 1877, ii. 358).

ginning of a *bilious fever*, and in *subacute* and *muscular rheumatism* it may often be used with great advantage. On the other hand, when in a fever it is desired not to produce a single excessive sweating, but simply to maintain moisture of the skin, jaborandi will hardly serve the purpose of the practitioner, and in *typhoid* or other asthenic fevers more or less danger of exhaustion attends its use.

In doses of from one-twelfth to one-fifteenth of a grain (0.005–0.004 Gm.), given every two to four hours, pilocarpine usually causes a decided increase in the secretion of urine, and is a valuable remedy in the treatment of *cardiac* and of *renal dropsies*. In rare cases albuminuria and even strangury * have followed this use of the drug, so that some caution would seem to be necessary in its employment in the early stages of *acute nephritis*. Nevertheless, we have seen it apparently successful in acute *suppression of urine*.

In the treatment of *pseudo-membranous laryngitis* and in *diphtheria* pilocarpine was at one time extensively used, under the belief that by increasing the secretion beneath the membranes it would loosen them; it has, however, failed to establish its value for this purpose. Ringer[38] has reported several cases of *unilateral sweating* cured by the use of full doses of pilocarpine given hypodermically. It has been used with asserted success in *alopecia*. Cheron affirms that, when given in doses of one-twelfth of a grain hypodermically, pilocarpine is very effective as a galactagogue, but Ch. Cornevin[39] found that in cows, at least, pilocarpine has no influence upon the quantity of milk secreted, though it increases the production of lactose.

Locally applied (half-ounce of the leaves) in the form of a poultice, jaborandi may sometimes produce local sweating only, but we have seen very marked and extraordinarily prolonged general sweating so caused.

ADMINISTRATION.—The fluid extract of jaborandi (EXTRACTUM PILOCARPI FLUIDUM, U. S.) may be given in doses of half a drachm to a drachm (2–4 C.c.), but is inferior to the alkaloid in being more uncertain in its action and more likely to cause nausea. The ordinary dose of the official *Pilocarpine Hydrochlorate* (PILOCARPINÆ HYDROCHLORAS, U. S.) is from one-eighth to one-third of a grain (0.008–0.02 Gm.). In larger doses it is capable of producing so severe sweating as to end in collapse. Even pilocarpine, however, is apt to cause vomiting, and we have found that when it is desirable to produce an excessive sweating for the purpose of breaking up a forming disease, much better results may be obtained by conforming to the following procedure than by giving pilocarpine unaided: let the patient, prepared for bed, take one dessertspoonful of a mixture containing, to the dessertspoonful, one-twelfth of a grain of pilocarpine hydrochlorate, five grains of antipyrin, and one to

* See Purjesz (*Deutsch. Arch. f. Klin. Med.*, xvii. 533); also Stumpf (*Deutsch. Arch.*, xvi.).

three minims of tincture of aconite-root ; soak the feet fifteen minutes in a hot mustard bath ; on getting into bed take a teaspoonful of the pilocarpine mixture, with a tumbler of very hot lemonade or whiskey punch ; repeating every twenty minutes the pilocarpine mixture until free perspiration sets in.

Antagonism with Atropine.—In 1875 Langley[40] called attention to the antagonism existing between jaborandi and belladonna. When the heart has been slowed or arrested by jaborandi, atropine will bring the rate of pulsation almost to normal ; the reverse of this also occurs, provided the amount of atropine previously applied has not been too great (Langley). Upon the sweat-glands the two drugs have also antagonistic powers, one being able to annul the action of the other (Fuchsinger). The same is true in regard to the salivary secretion (Langley). This antagonism between atropine and jaborandi is affirmed by H. Larvand to extend to the intestines and pupil. In belladonna-poisoning the alkaloid has been used with no advantage in very small dose,[41] but in a case in which nine-tenths of a grain of atropine had been taken, nine grains of pilocarpine are said to have been injected hypodermically in between one and two hours with success (Purjesz[42]). L. Juhász[43] reports a case in which it was estimated that about one and a half grains of atropine were taken, followed in half an hour by vomiting ; four and a half grains of pilocarpine were injected in about seven hours, with a favorable result. Hofferts[44] reports a case in which seven and a half grains of extract of belladonna were ingested, and nearly two grains of pilocarpine given, with recovery.*

SPIRITUS ÆTHERIS NITROSI—SPIRIT OF NITROUS ETHER. U. S.

Sweet spirit of nitre is an alcoholic solution of *ethyl nitrite*. It is soluble in all proportions in water and alcohol, and has a neutral reaction, is a volatile, inflammable liquid, of a pale yellow color inclining slightly to green, having a fragrant, ethereal odor, free from pungency, and a sharp, burning taste. It has the specific gravity 0.836 to 0.842, and contains 4.3 per cent. of its peculiar ether. It should not be long kept, as it becomes acid by age.

Sweet spirit of nitre when taken freely in the form of fumes may cause symptoms of nitrous acid poisoning. Thus, as produced by its inhalation, D. R. Brown[45] noted very pronounced cyanosis of the face and hands, mental confusion, headache, cold extremities, excessive muscular weakness, very rapid, feeble pulse, a slow, regular respiration which on the least exertion became hurried and accompanied by a painful sense of oppression in the chest and by cardiac distress. When the spirit is taken by the mouth, the alcohol in it asserts its physiological powers. Thus, in a child three years old, killed in twelve hours by four

* For other cases of like import, see *Lancet*, 1890, ii. ; also *Therap. Gaz.*, 1887.

ounces of the spirit, the symptoms closely resembled those of alcoholic poisoning, with the addition of vomiting and purging.*

The therapeutic dose of nitre is somewhat calmative, and has some influence, though not a very great one, in increasing the secretions of the skin and kidneys. It is a very popular remedy, especially useful in the case of children suffering from adynamic fevers with such nervous symptoms as starting, jerking, mental excitement, etc. If the patient be kept on his feet and cool instead of being warmly covered in bed, the single large dose of the spirit of nitrous ether acts as a mild diuretic. When a diaphoretic action is required, small doses should be exhibited at short intervals. Thus, for a child one year old a teaspoonful may be put in five ounces of water and a tablespoonful be given every half to one hour. The adult dose is one to two fluidrachms (4–7 C.c.).

Spirit of Mindererus (LIQUOR AMMONII ACETATIS. U. S.—*Solution of Ammonium Acetate*) is a colorless, odorless liquid, prepared by saturating dilute acetic acid with ammonium carbonate. It was formerly used to a considerable extent in the treatment of *adynamic fevers* as a mild stimulant and diaphoretic, but has very properly fallen into disuse except as a vehicle for more powerful remedies. The dose usually given is one to two tablespoonfuls (7.5–15 C.c.), but two ounces (60 C.c.) of it may be exhibited at one time.

Before the introduction of jaborandi, probably the most useful and most efficient known diaphoretic was *Dover's Powder* (PULVIS IPECACUANHÆ ET OPII, U. S.), which contains one grain of opium, one grain of ipecacuanha, and eight grains of sugar of milk. When, as in some cases of *acute rheumatism*, it is desired at the same time to allay pain and increase the action of the skin, Dover's powder may be exhibited in doses of from three to five grains (0.2–0.3 Gm.) every two, three, or four hours, *pro re nata*, in capsules or pill. Given in a single large dose,—ten grains (0.7 Gm.),—especially when aided by proper measures and other diaphoretics, it is efficient in producing a free perspiration, and may thus be used in forming acute colds, etc. In the intense suffering which sometimes results from sudden *suppression of menstruation*, Dover's powder, by relieving pain and aiding in the production of diaphoresis, often acts most favorably.

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* Case, *Lancet*, 1878, ii. Christison reports a case of a woman whose death was attributed to sweet spirit of nitre.

FAMILY VI.—EXPECTORANTS.

UNDER the present heading we propose to discuss not only true expectorants,—that is, those medicines which have the power of influencing diseased conditions of the respiratory mucous membranes,—but also various substances and even various procedures which are employed for the relief of pulmonic conditions.

Cough.—When from disease or from other causes obnoxious materials, be they secretions or foreign matters, accumulate in the bronchial tubes, cough is necessary for their expulsion, so that in a large proportion of cases no treatment of cough is desirable. On the other hand, there are cases in which, owing to excessive irritability of the pulmonic mucous membrane, the amount of cough is out of all proportion to the amount of material to be expelled. Under these circumstances the symptom is not only annoying, but also, by irritating the mucous membrane of the lungs and by exhausting the patient, directly harmful. In another set of cases, owing to muscular weakness and to lack of irritability of the mucous membrane, the cough is not sufficient for the expelling of the secretions, which gradually accumulate in the lungs, fill up the bronchial tubes, and finally, it may be, cause death by a process comparable to that of drowning.

It is plain that the medical practitioner must study in each individual case the relations between the cough and the amount of work required; so that if the cough be excessive it may be allayed, if it be insufficient it may be stimulated. For the purpose of allaying cough, soothing vapors or liquids may be applied to the respiratory mucous membrane by inhalations, but in the majority of cases internal anodynes are necessary.

In some instances the cough is maintained by an excessive irritability in the upper throat and air-passages, so that demulcents such as liquorice are very useful, or relief may be obtained by sipping a mixture composed of glycerin and whiskey, each one part, with two to four parts of water.

The anodyne substances which are employed for the relief of cough are hydrocyanic acid, belladonna, hyoscyamus, chloroform, the bromides, and heroine. The action of hydrocyanic acid is too brief for the remedy to be of practical value. Belladonna, unless locally applied by means of atomization, is very uncertain in its action and of entirely secondary importance; superior to it is hyoscyamus, although even full doses of this remedy often are ineffective. Chloroform, in doses of ten to fifteen minims, sometimes acts most happily, but must be given at very

short intervals on account of the fugaciousness of its influence, and is more useful in combination than alone. The bromides in full doses are often effective, and may well be combined with chloroform ; in some cases they are too depressant. Much more certain in its influence than any remedy yet mentioned is opium ; its tendency to check secretion forbids its use, however, in a very large proportion of cases, notably in those in which there is persistent dryness of the bronchial mucous membrane, whether this dryness represents the first stage of an acute bronchitis or whether the case be one of a continuing subacute bronchial irritation so frequent in neurotic individuals. Moreover, the usefulness of opiates is further limited by their tendency to derange digestion, and in chronic cases by the danger of forming the opium habit. Under these circumstances the diacetic ester of morphine (heroine) is very valuable.

We know of no method of increasing the irritability of the pulmonic mucous membrane when impaired. In such cases, if the loss of irritability be, as it usually is, dependent on general atony, strychnine and cocaine may be administered in full doses, and are sometimes very serviceable. In an acute case, with failure to expel the secretion, as in the *suffocative catarrh* of infants, life may sometimes be saved by mechanical treatment. Stimulating emetics are often of the greatest service in freeing the bronchial tubes of secretion. On various occasions we have resuscitated young children after they had become completely comatose and lost the ability of swallowing from asphyxia due to suffocative catarrh, by the following procedure, which was suggested to us by the well-known reflex spasmodic contraction of the respiratory muscles produced by a dash of cold water on the chest :

Provide three tubs, one empty, one containing ice-water, and one with water at about 115° F. Hold the naked body of the child over the empty tub, and dash over the upper thorax a ladleful of the hot water, followed immediately by one of the cold water. So soon as the color of the skin has begun to change under the respiratory gaspings, and some evidences of consciousness appear, dip the body of the child momentarily in the hot water, when the scream produced by the pain will usually fill the lungs with air. In this procedure the hot water is used alternately with the cold water to prevent chilling of the body as well as to increase the shock.

To allay Spasm.—When a spasm affects the laryngeal muscles acutely it may often be put an end to by an emetic dose of ipecacuanha or, in a very robust subject, of lobelia ; but in some cases, especially in so-called *laryngismus stridulus*, the exhibition of an anæsthetic may be necessary for the saving of life. In such cases chloroform should be selected on account of the locally irritating influence of ether. Amyl nitrite in alarming cases often acts most happily. For the prevention of the recurrence of these spasms the various anodynes mentioned above may be employed. The most generally successful is the bromide, which in *spasmodic croup* should be given repeatedly in full doses. Local applications of belladonna—the smoking of belladonna cigarettes—are often very useful.

In extreme cases of asthmatic bronchial spasm relaxation may be obtained by the exhibition, in robust cases, of lobelia in full doses, by smoking belladonna or stramonium cigarettes or pipes,* by the inhalation of amyl nitrite or chloroform, or by hypodermic injections of morphine or of heroine hydrochlorate.

Local applications may be made to the lungs in the form of vapor or of fine spray obtained by the so-called pulverization of water.

Atomization consists in breaking up by a mechanical contrivance watery solutions of a medicinal substance into a fine spray. At one time it was believed that in this way the finest ramifications of the bronchial tubes could be reached, but the method has gradually passed out of use except for cases in which the disease is in the fauces, larynx, or trachea. In using atomization it must be remembered that it is only a means of making a local application to a certain part, so that the rules governing the choice of drugs to be employed are precisely those affecting local applications to other than the respiratory mucous membrane.

By atomization warm water may be applied as a diluent and as a soothing application, its soothing properties being capable of increase by the addition of cocaine, opiates, or other narcotic remedies. By atomization stimulant substances, such as ammonium chloride, also benzoates, carbolates, or other antiseptics, may be brought in contact with a diseased mucous membrane. When there is excessive secretion, as in *bronchorrhœa*, or hemorrhage, as in *hæmoptysis*, the practitioner may use in the atomizer such astringents and hæmostatics as—tannic acid, one to twenty grains to the fluidounce ; alum, from five grains to the fluidounce to a saturated solution ; iron, Monsel's solution, five to fifteen drops to the fluidounce. In all cases in which strong local applications are being made to the lungs the occurrence of severe cough is an indication that the application is causing much irritation.

TRUE EXPECTORANTS.

From a therapeutic point of view acute bronchitis is divisible into three stages : first, that of extreme dryness of the mucous membrane and tightness of cough ; second, that in which secretion is about to be established ; third, the final stage, in which expectoration is free. In an

* There are upon the markets numerous proprietary mixtures for the relief of asthma by smoking ; most if not all of them consist of powdered belladonna or stramonium, mixed with potassium nitrate and sometimes other substances. Clinical experience has shown that the efficiency of these powders is increased by the presence of arsenic, which probably acts by stimulating the bronchial mucous membrane to secrete freely. The following formula, taken from an old Pharmacopœia of the Philadelphia Hospital, we have found to yield a very efficacious paper.

CHARTA ARSENICALIS COMPOSITA (*Compound Arsenical Paper*). ℞—Belladonnæ fol., gr. xcvi ; Hyoscyami fol., Stramonii fol., āā gr. xlviii ; Extr. opii, gr. iv ; Tabaci, gr. lxxx ; Aquæ, Oj ; M., ft. sol. et add. Potas. nit., gr. clx ; Potas. arsenit., gr. cccxx. Saturate bibulous paper and dry for use. Roll the paper into cigarettes, one of which is to be smoked two to six times a day until relief is afforded or some giddiness is produced.

The expectorant dose is one-twelfth of a grain (0.005 Gm.), repeated every two or three hours.

EXPECTORANTS OF THE SECOND GROUP.

AMMONII CHLORIDUM—AMMONIUM CHLORIDE. U. S.

Ammonium Chloride occurs in large concavo-convex plates, white, translucent, tough and fibrous, free from odor, but having a sharp, saline taste, and soluble in three parts of cold and one part of boiling water.

THERAPEUTICS.—Ammonium chloride is a powerful irritant, concerning whose poisonous properties there is great diversity of statements. Oesterlen affirms that he has seen two ounces of the salt taken by man without the production of more serious results than violent gastro-intestinal pain and diarrhœa, whilst older observers state that two drachms of the salt are sufficient to cause death in a dog. According to Arnold, thirty grains will kill a rabbit in ten minutes; but Rabuteau found that one drachm injected intravenously produced in the dog only vomiting, muscular weakness, temporary paralysis of the hind legs, and general prostration, lasting four or five hours. After absorption it shares the general physiological activity of the ammoniacal salts. When given for a length of time in very large doses it affects the general nutrition. We have seen extreme prostration and a typhoid condition apparently produced by the taking of half an ounce per diem for some days, whilst great prostration, with an eruption of bloody blebs, hæmaturia, and hemorrhages from the mucous membranes, has been reported by Isham as caused by the continuous use of the drug.

These symptoms are concordant with the statements of Sundelin, that the blood suffers especially and loses its plasticity under the action of the drug. In an elaborate series of analyses, F. W. Böcker[1] determined that its long use is accompanied by a decided decrease in the solids of the blood,—an observation confirmed by Arnold. Both Böcker and Rabuteau[2] found that in healthy man it notably increases the urea and other solids of the urine except uric acid, so that when taken in large amount and continuously it evidently has a positive influence on the chemical movements of the organism.

According to Rabuteau, ammonium chloride is freely secreted by the salivary glands, but chiefly escapes from the kidneys, almost all the salt taken being recoverable from the urine.

Although there is sufficient reason for believing that ammonium chloride especially affects the respiratory mucous membrane, the statement of Böcker, that it hastens very greatly the nutritive changes and the exfoliation of the epithelium in all mucous membranes, is in accord with clinical experience as to its value in various gastro-intestinal conditions. In Germany more than in this country it has been extensively used in the treatment of *chronic gastric* and *intestinal catarrhs*. The statement of W. Stewart,[3] made in 1870, that it is an effective remedy

in *chronic torpor of the liver* and *chronic hepatitis*, has been sustained by subsequent clinical experience, and it has become a standard remedy in these affections and in *catarrhal jaundice*. As an expectorant ammonium chloride is useful in an *acute bronchitis* when free secretion has just been established. In *chronic bronchitis* it should be administered from time to time when the secretion is not very free.

Ammonium chloride was at one time frequently given in *intermittent fever*, but has failed to sustain itself. Another old use was for relieving pain in *neuralgia*, especially of the ovarian variety. Thirty grains of it were administered in combination with two to five drops of tincture of aconite root, repeated in half an hour if necessary. In our hands this treatment has not given satisfaction. The expectorant dose of ammonium chloride is five to ten grains (0.3–0.6 Gm.) every three hours, in at least two ounces of water. The dose in hepatic diseases is twenty to thirty grains (1.3–2 Gm.) in four or five ounces of water, three or four times a day, administered when the stomach is empty.

EXPECTORANTS OF THE THIRD GROUP.

GRINDELIA. U.S.

This is the leaves and flowering tops of Grindelia robusta and of Grindelia squarrosa, plants inhabiting the extreme western portions of North America. In commerce the whole herb, including the stems, roots, and floral heads, is sold. The taste is warmish, peculiar, and very persistent.* The presence of a crystalline alkaloid in grindelia has been asserted by several investigators, but at present it seems probable that its activity depends upon a turpentine-like volatile oil.

Physiological Action.—The toxic powers of grindelia are said to be so feeble that three drachms of the fluid extract are required to kill a rabbit. Concerning its physiological action we have little definite knowledge; according to Buffington, it produces narcosis with dilated pupils by a cerebral influence, but acts more powerfully in paralyzing the nerves of sensation and the sensory side of the cord, and finally attacks both the motor cord and nerves. Dobroklowski asserts that it acts upon the motor nerves and the muscles. Buffington affirms that it causes in warm-blooded animals a slowing of the action of the heart by stimulating the inhibitory apparatus, and an elevation of the blood-pressure by stimulating the vaso-motor centres. Dobroklowski states that the large but non-toxic doses increase the pulse-rate as well as the arterial tension; also that these phenomena not being affected either by isolation of the heart from the nervous system, by the previous use of atropine, or by division of the spinal cord, they must be caused by a direct influence upon the heart or the peripheral vessels. Dobroklowski further affirms that in toxic dose the drug depresses the

* See *Centralbl. f. Med. Wissens.*, 1885, xxiii.; *Amer. Journ. Med. Sci.*, Jan. 18, 1886; *Lond. Med. Rec.*, March, 1886.

pulse-rate and the arterial tension, and finally arrests the heart in diastole.

THERAPEUTICS.—Grindelia has not been employed for its effect upon the circulation, and in the doses used in medicine it appears to exert no distinct influence upon the heart or arteries. It has been largely used, often with alleged excellent results, in *asthma*, and in *bronchitis* associated with a tendency to bronchial spasm. It is probable that in these cases it not only has a relaxing influence, but also stimulates the mucous membrane, and even in *chronic bronchitis*, especially of the aged, it is said to do good. It has been employed in *whooping-cough*. Its active principles are probably excreted by the kidneys; hence after large doses there are sometimes evidences of renal irritation, and in chronic *catarrh of the bladder* good has been effected by its stimulant influence upon the mucous membranes of the viscus. It has also been employed as a local application, with alleged good results, in *vaginitis*. The dose of the fluid extract (EXTRACTUM GRINDELIÆ FLUIDUM, U. S.) is from twenty to sixty minims (1.2–3.7 C.c.). The fumes of burning grindelia are sometimes inhaled with alleged relief in *asthma*. The plant should be steeped in a solution of nitre, dried, and burnt upon a plate, or may be smoked in cigarettes or in a pipe.

BALSAMUM PERUVIANUM, U. S., *Balsam of Peru*, is obtained from Toluifera Pereiræ, a tree of Central America. This balsam is a viscid, honey-like, fragrant, brownish fluid, of a warm, bitterish taste, which has been shown by Bräutigam and Nowack[4] to be practically devoid of antiseptic properties. According to Frémy, it contains not benzoic, but cinnamic acid. It has been used in *chronic catarrhs* of the respiratory and the genito-urinary systems, in doses of half a fluidrachm (2 C.c.).

BALSAMUM TOLUTANUM, U. S., *Balsam of Tolu*, is obtained from Toluifera Balsamum, a tree very closely allied to that which yields the balsam of Peru. Balsam of Tolu is at first a thick, viscid fluid, but by time it is converted into a hard, translucent, resinous solid. Its odor is highly fragrant and its taste vanilla-like. It contains cinnamic acid and a volatile oil, and its medical properties are the same as those of the balsam of Peru. On account, however, of its grateful taste, it is preferred to the latter, and is very much used to flavor medicines, especially cough-mixtures. In large doses, twenty to thirty grains (1.3–2 Gm.) every three hours, it may be of some value in *chronic bronchitis*, but as generally used its preparations are simply agreeable vehicles. The dose of the tincture (TINCTURA TOLUTANA—ten per cent., U. S.) is one-half to one fluidrachm (2–4 C.c.); of the much more frequently used syrup (SYRUPUS TOLUTANUS, U. S.), half a fluidounce (15 C.c.).

ALLIUM, U. S., or *English Garlic*, the clove of Allium sativum, contains a volatile oil, which in small doses is a stimulant to digestion, and

is also used as a stimulating expectorant in the advanced stages of obstinate *bronchitis*, and in the *acute bronchitis* of infants, when the powers of the system begin to flag. The oil of garlic is further believed to have the ability to stimulate the expulsive function of the small bronchial tubes, and is certainly a powerful rubefacient and a decided nervous stimulant. For these reasons, garlic poultices are a favorite application in the acute *suffocative catarrh* of infants, and are not rarely applied to the spine, legs, and feet in general *infantile convulsions*. They are made by simply reducing the garlic to a pulp by pounding. When a continuous application is desirable to the delicate skin of an infant, as in catarrh, it is generally necessary to reduce their strength with flaxseed meal. The dose of the syrup (SYRUPUS ALLII, U. S.) for a child a year old is one fluidrachm (4 C.c.).

SCILLA, U. S., or *Squill*, is one of the most used of the stimulating expectorants, coming especially into play in the advanced stages of ordinary *bronchitis*. The syrup (SYRUPUS SCILLÆ, U. S.) is the favorite expectorant preparation. As it contains acetic acid, it is incompatible with ammonium carbonate. *Compound Syrup of Squill*, or *Coxe's Hive Syrup* (SYRUPUS SCILLÆ COMPOSITUS, U. S.), contains one grain of tartar emetic to the ounce, and is therefore sedative to the circulation, although stimulant to the bronchial mucous membrane. It is not suitable for young children, although it has been much used in spasmodic *croup*. The dose of the simple syrup is one-half to one fluidrachm (2–4 C.c.); of the compound, twenty to forty drops (1.2–2.5 C.c.), according to age, repeated every twenty minutes until it operates.

PIX LIQUIDA. U. S.—*Tar* is a black semi-liquid substance, of peculiar odor and taste, obtained by the destructive distillation of various species of pine. The tar used in this country is almost exclusively the product of the Pinus palustris of North Carolina and other of the Southern States. In composition it is very complex, containing pyroligneous acid, creosote, empyreumatic oil, and a number of more or less peculiar principles. When distilled, it yields an oily liquid, known as *oil of tar*, and a solid, black residue, *pitch*. It is freely soluble in alcohol, ether, and the fixed and volatile oils, and also to a slight extent in water. The physiological action of tar resembles that of creosote. According to Taylor, the *oil of tar* has produced death in man. To cause death, tar itself would have to be ingested in enormous quantity, since a sailor (according to Stillé) recovered after taking between a pint and a quart of it. It is used internally solely in the advanced stages of obstinate *acute bronchitis*, or in *chronic bronchitis*. Locally, it is much employed in chronic diseases of the skin, as a stimulant application in the form of the official ointment (UNGUENTUM PICIS LIQUIDÆ, U. S.,—equal parts). In many cases this is too severe, and the strength must be reduced. Hebra states that if it be applied too freely enough of the tar may be ab-

sorbed to darken the color of the fæces and the urine, and even to cause gastric irritation and black vomit. For internal administration the best preparation is the *Syrup of Tar* (SYRUPUS PICIS LIQUIDÆ—7.5 per cent., U. S.),—dose, one to two fluidrachms (3.7–7 C.c.).

AMMONIACUM. U. S.—*Ammoniac.*—This gum resin is the concrete juice of the Persian plant Dorema Ammoniacum ; it is a local irritant capable of causing vomiting and purging, which was formerly used to a considerable extent in *chronic bronchitis* with excessive secretion, but is now almost out of vogue. The dose is from twenty to thirty grains (1.3–2 Gm.) of the emulsion (EMULSUM AMMONIACI—four per cent., U. S.), one or two tablespoonfuls may be given. EMPLASTRUM AMMONIACI CUM HYDRARGYRO, U. S., contains mercury and sulphur, and is employed as a local stimulant, alterative, and discutient in *scrofulous* and *syphilitic swellings, enlarged joints*, etc.: its external use is said to have caused salivation.

SENEGA. U. S.—*Senega.*—The root of Polygala senega, a small, indigenous, herbaceous perennial, is several inches long, very much contorted, of a peculiar feeble odor, and a taste at first sweetish but afterwards acrid. It is distinguished by a keel-like line, shorter than the root, and presenting the appearance as if a string were drawn tightly under the bark from end to end. It contains saponin (*polygalic acid* of older chemists), and perhaps a second active principle, *senegin*. It is an actively irritant substance which has been much used in America in very advanced stages of *acute bronchitis*, and in *chronic bronchitis* with free expectoration. In overdoses it produces vomiting and purging. As an expectorant it is not as effective and reliable as various other members of the class. The dose of the fluid extract (EXTRACTUM SENEGÆ FLUIDUM, U. S.) is from ten to fifteen drops (0.6–1.2 C.c.) ; of the syrup (SYRUPUS SENEGÆ, U. S.), a fluidrachm (3.7 C.c.).

TEREBENUM. U. S.—*Terebene* is a clear, colorless liquid, insoluble in water, isomeric with turpentine, and of a peculiar odor, somewhat resembling that of freshly sawed pine wood. It is prepared by the action of sulphuric acid upon oil of turpentine.

Terebene, one of the most effective of the stimulant expectorants, was first recommended by William Murrell.[5] It is very useful not only in *chronic bronchitis*, but also in the *acute* disease after the earlier stages have passed by. As an expectorant it is nearly equivalent to the oil of eucalyptus, but is more stimulating. It has also been employed with asserted good results in *dyspepsia*, especially in the flatulent intestinal variety, and may be used in chronic or subacute *inflammations of the genito-urinary tract.* Its action upon the general system has not been investigated, but probably resembles that of oil of turpentine. From twenty to forty minims (1.2–2.5 C.c.) of it may be given to the adult in the course of twenty-

four hours. It lends itself well to use by inhalations, either by atomization of water containing it or by vaporization from hot water. The vapor should be as concentrated as can be borne without exciting cough.

OLEUM SANTALI, U. S., *Oil of Sandal Wood*, is a pale yellowish, strongly pungent, aromatic, and spicy volatile oil, obtained from the wood of the Santalum album. It is a stimulant or irritant to the various mucous membranes, and while its general action upon the system is not known, it is a very valuable remedy in *chronic bronchitis* and in the advanced stages of *acute bronchitis*, and also in the advanced stages of *gonorrhœa*. It seems to be more stimulating than is the oil of eucalyptus. From ten to twenty drops (1.2–2.5 C.c.) may be given every three or four hours in capsules, emulsions, or on sugar.

Among the most valuable of the stimulant expectorants are the *oil of eucalyptus* and *creosote*. (See pages 550 and 565.)

SULPHURETTED HYDROGEN.—In 1886 Bergeon[6] proposed a method of treating *phthisis* by filling the large intestine with sulphuretted hydrogen diluted with pure carbonic acid gas. After an extraordinary but very brief popularity the method has fallen into such complete desuetude that it is only necessary here to refer to the tenth edition of this treatise for details.

Sulphuretted hydrogen is, however, a valuable remedy in the treatment of purulent *pulmonic catarrhs*, whether of tubercular or other origin. When, under any circumstances, a bronchial catarrh is accompanied by very free expectoration the remedy may be useful in relieving the mucous membrane. We have also found it of service in *chronic gout*, when administered persistently for months. The method of administration employed by Bergeon was barbarous and absurd. The sulphuretted hydrogen may be given by the mouth in the form of a natural sulphur-water or, better, by means of water saturated with sulphuretted hydrogen and carbonic acid gas. The dose of the saturated solution is two to four ounces (60–118 C.c.), three or four times a day. In some cases it produces digestive disturbance, and its use has to be abandoned. That the gas is absorbed and eliminated by the lungs is proved by the very perceptible odor upon the breath.

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FAMILY VII.—EMMENAGOGUES.

EMMENAGOGUES are medicines which are employed to promote the menstrual flux. In the great majority of cases amenorrhœa is due to some local pelvic disease or general constitutional condition, the removal of which relieves the symptom. There are a few substances which appear to act directly as stimulants to the uterine mucous membrane, although they are notoriously uncertain in their effectiveness.

When *amenorrhœa* is a symptom of chlorosis or due to other forms of anæmia, full doses of iron should be given. With iron may be combined the gum-resin *myrrh*, as in the compound mixture of iron (MISTURA FERRI COMPOSITA, U. S.—*Griffith's Mixture*). Dose, from one to two fluidrachms (4–7 C.c.), three times a day. When *atonic amenorrhœa* exists with constipation, aloes should be given along with the other emmenagogues. Ordinarily it should be administered in repeated doses (three times a day) of such size as will produce daily one or two soft, semi-liquid stools. At the menstrual period advantage may sometimes be derived from the administration of a full purgative dose.

POTASSIUM PERMANGANATE, originally recommended by Sydney Ringer as an emmenagogue, has been very highly commended by Fordyce Barker and other physicians.* According to Barker, the permanganate is not to be employed when menstruation has been arrested by grave constitutional or local disease, or suddenly by cold, moral shock, or acute disease. Abortifacient properties have been attributed to it, and cases are reported in which abortion has followed its administration.†

Therapeutic doses of the permanganate must be entirely decomposed in a very short time after they reach the stomach, so that any action which the drug exerts upon the general system is due to the manganese oxide; indeed, the ordinary *black manganese oxide* has been affirmed by various practitioners to be as active an emmenagogue as is the permanganate. We have employed these agents to a limited extent in functional *amenorrhœa*, sometimes with, sometimes without, success. The only difference which we have been able to perceive in their action is that the permanganate is the more irritant to the stomach. The dose of either preparation may be set down as one to two grains (0.06–0.13 Gm.),

* See *Therap. Gaz.*, ii. and iii.

† See J. L. Watkins (*Therap. Gaz.*, ii.), and S. B. Sperry (*Ibid.*, iii.).

—always administered after meals, in order to avoid, as far as possible, gastric irritation. Cases of severe gastritis produced by the permanganate have been reported.[1]

CANTHARIDES is a very decided uterine stimulant, and is much used in emmenagogue mixtures. From two to five minims (0.13–0.3 C.c.) of the tincture may be given three times a day; if no unpleasant symptoms arise, the dose may cautiously be increased to six minims, the production of strangury being, of course, sedulously avoided.

GUAIAC, as an emmenagogue, is much less stimulating than cantharides, and is believed by some to be especially useful in *rheumatic dysmenorrhœa*. In this affection, full doses of the ammoniated tincture should be given. The following formula, adapted from that of Dewees, known as *Dewees's Emmenagogue Mixture*, is probably the most effective combination ever made in *atonic amenorrhœa*. The proportion of the various ingredients should be varied to suit the exigencies of individual cases.

℞ **Tincturæ ferri chloridi, f℥iii; Tincturæ cantharidis, f℥i; Tincturæ aloës, f℥ss; Tincturæ guaiaci ammoniatæ, f℥iss; Syrupi, q. s. ad f℥vi. S.—Tablespoonful three times a day.**

SABINA. U. S.—*Savine.*—The dried tops of Juniperus sabina, a juniper, native of the south of Europe and the Levant, contain a turpentine-like volatile oil. This oil is a powerful irritant. When taken in sufficient dose, it produces severe abdominal pain; incessant vomiting and bloody purging; diminution or even suppression of the urine, which is often albuminous and bloody; disordered respiration; symptoms of disturbed innervation, such as unconsciousness, stertorous breathing, and convulsions or convulsive tremblings; the scene closing by death in collapse. In pregnant females, abortion, accompanied by violent flooding, almost always occurs before the fatal issue. After death, signs of gastro-intestinal inflammation are generally present, but in some instances these are wanting, and in one case reported by Letheby[2] pulmonary apoplexy and congestion of the brain were the chief lesions.

In rare cases of *menorrhagia* dependent upon uterine relaxation, the oil of savine is useful in doses of from five to ten drops (0.3–0.6 C.c.). It owes its importance to the frequency of its domestic use as an abortifacient,—a use which is accompanied by the gravest danger to life and has often ended in death. The dose of the volatile oil (OLEUM SABINÆ, U. S.) is from five to ten minims (0.3–0.6 C.c.).

RUE.—The leaves of Ruta graveolens, or common garden rue, contain a volatile oil whose properties are similar to those of oil of savine. It has been used in Europe for the production of criminal abortion, but seems to be less employed than is the oil of savine, and to be less dangerous.

as we have met with no records of death from it except that of a man weakened by dysentery.* According to M. Hélie, taken internally, in large doses, it causes violent gastric pains, excessive and sometimes bloody vomiting, profuse salivation and swelling of the tongue, great prostration, confusion of mind, and convulsive twitchings, with, in pregnant women, abortion.

TANACETUM. U. S.—The common tansy of the gardens, Tanacetum vulgare, in the form of decoction, or of its volatile oil, is sometimes used as a stimulant emmenagogue or for the purpose of producing abortion, but is a very unsafe remedy. When taken in sufficient amount it causes abdominal pain, vomiting, loss of consciousness, and violent epileptiform convulsions.† The minimum fatal dose of the oil of tansy is not known, but in two cases[3] a teaspoonful of the oil produced violent epileptiform convulsions, and the same amount is said to have caused death. Recovery is stated to have occurred after one and a half fluidrachms ;[4] also after three fluidrachms.[5] The action of the oil upon the lower animals has been studied by Guillery.[6] In frogs the most important effects which it was found to produce were paralysis of the peripheral endings of the motor nerves, with early appearance of post-mortem rigidity ; and paralysis of the vaso-motor centre of the medulla and of the inhibitory cardiac apparatus, with at last paralysis of the heart itself. In warm-blooded animals the oil produced symptoms precisely similar to those which it causes in man. After section of the spinal cord the convulsions did not occur in the hind legs : they are therefore of cerebral origin. The arterial pressure was not affected until death was at hand : so that it is evident that the drug has little action upon the heart.

OLEUM HEDEOMÆ. U. S.—Under the name of *oil of pennyroyal*, in the United States, the oil of the Hedeoma pulegioides is used as a stimulating emmenagogue in domestic practice, but has very little power. Two fluidrachms taken by a young woman produced vertigo, faintness, muscular weakness, frequent feeble pulse, cold skin, and cold extremities (C. A. Bryce[7]). Dose, from two to ten minims (0.12–0.6 C.c.). In Europe the oil of Mentha pulegium is known as *oil of pennyroyal*.

APIOL.—Apiol is a peculiar non-nitrogenous, yellowish, oily liquid, which is obtained from the root of the Apium petroselinum, or common parsley. According to its discoverers, Joret and Homolle,[8] one gramme

* Case of G. F. Cooper (*Med. Examiner*, N. S., ix. 720).

† For references to fatal cases, most of which have occurred in the United States, see *U. S. Dispensatory*, also Guillery (*loc. cit.*). Guillery believes that the symptoms caused by the oil and by tansy tea are different. In a case of poisoning by the leaves, however, reported in the *Nashville Med. and Surg. Journ.*, 1879, xxiii., the symptoms were those alleged to be characteristic of oil-poisoning; and the oil probably is the only active principle of the drug.

of it will produce in man a cerebral excitation very similar to that induced by coffee, without other symptoms. In doses of from two to four grammes it causes a species of intoxication, with vertigo, ringing in the ears, and severe frontal headache,—a group of symptoms very similar to those seen in cinchonization.

Apiol has been used to a considerable extent as an antiperiodic, but it is certainly of very inferior rank. It was originally recommended in *amenorrhœa* by Joret and Homolle, who exhibited three or four grains twice a day for a week preceding the time in which the return of menstruation was due. Whenever any symptoms of the menstrual molimen appear, fifteen grains of it should be administered in the course of three or four hours. It is always given in capsules, each of which, as imported from France, usually contains one-quarter of a gramme (3.9 grains).

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6. Guillery . . . . B. A. R. B., 1878, xii.
7. Bryce . . . . . Southern Clinic, vi. 323.
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FAMILY VIII.—OXYTOCICS.

OXYTOCICS are those remedies which are employed during or directly after parturition, to increase the uterine action. Of the few drugs which have claims for position in the present class, quinine has already been fully considered; it apparently differs entirely from the other known oxytocics in not producing continuous tetanic spasms of the uterus, and is therefore the safest stimulant to parturition at our command. The peculiar dangers which beset the use in labor of drugs which cause uterine tetanus will be fully discussed in the article upon ergot.

ERGOTA—ERGOT. U.S.

Ergot is a blackish body, one to two inches in length, irregularly cylindrical, grooved along one side, and very generally curved; it is composed of very thick walled microscopic cells, containing oil-drops but no starch. As was first demonstrated by Tulasne,[1] ergot is the sclerotium of the Claviceps (C. purpurea, Tulasne) which infests the grain of Secale cereale, or rye.

Among the lowest of vegetable organisms, and distinguished from all other plants by the absence of chlorophyll, are the fungi. There are in most cases two distinct states or stages in the life of a fungus: in the first of these, the vegetating period, it exists as a *mycelium*, a usually filamentous mass or flocculus, whose sole function is to grow and increase; in the second stage the *thallus*, or ordinary fungus or mushroom, is formed, and to it is assigned the function of developing reproductive bodies, after whose maturation it perishes. Between these stages there is in some fungi an intermediate one, in which the plant exists as a *sclerotium*. The genus Claviceps comprises a number of parasitic fungi, which develop in the pistils of the various species of Gramineæ. The first appearance of the ergot is in the flower of the rye, at the base of whose pistil there arises a minute flocculent mass of mycelial filaments. These filaments, continually growing and invading all parts of the tissue of the pistil, at last form of it an irregular whitish body, at the base of which after a time appears a dark-colored body, the sclerotium, which continues to grow, lifting up the diseased and withering mass formed out of the original pistil, and finally developing into a perfect ergot. If a fresh, living ergot be placed in a damp, warm place, after a time little cracks will appear in its surface, and through these cracks little round bodies will project, and finally be raised up on stalks and constitute perfect thalli,—minute fungi, which finally produce spores.

Ergot is an exceedingly complex substance, containing nearly thirty-five per cent. (Legrip) of an inert fixed oil, but of whose active principles

we have no definite knowledge. The most condensed representative of the activities of the drug is the watery extract.*

PHYSIOLOGICAL ACTION.—*Local Action.—Absorption and Elimination.*—The preparations of ergot have a very feeble local action, but their irritant properties are sufficient to interfere with their hypodermic use, and sometimes to make them disturb the stomach. They yield their active principles readily to absorption, but concerning the fate of these bodies in the organism we have no knowledge.

General Effects.—Even the largest therapeutic doses (an ounce of the fluid extract) produce in man no perceptible symptom save some nausea. In a number of cases death has resulted from abortion caused by large doses of ergot,† but we know of but two instances of serious poisoning in a non-pregnant person.‡

In the first case gastric irritation, thirst, diarrhœa, burning pain in the feet, and convulsions are said to have preceded death. In the second case (G. S. Oldright[2]), two hours after taking the drug (amount not stated) there were developed tingling in the fingers and feet, cramps in the legs, arms, and chest, with dizziness and weakness; the pupils were dilated, the pulse was very small, and a feeling of coldness was complained of. These symptoms were relieved by the administration of stimulants and the use of external heat; after a time they recurred with greater violence; finally, under the reinstitution of the measures previously employed, the face became intensely congested and purplish red, pain in the head was felt, the patient seemed much excited, and convulsions were feared, but did not occur; there was some diarrhœa, with dark gray stools.

According to Diez (quoted by Stillé), the principal effects of poisonous doses of ergot are in the lower animals profuse salivation, vomiting, dilatation of the pupils, hurried breathing, frequent pulse, cries, trembling, staggering, paraplegia, in some cases diarrhœa and urgent thirst, convulsions, and death.

In the experiments of S. A. Wright[3] the paralysis was much more marked than were the spasms: in some cases the special senses seemed to be destroyed, and coldness of the surface was a very prominent symptom. Wright found that the intravenous injection of a strong infusion caused immediate dilatation of the pupils, great increase in the rate of the cardiac pulsations, paralysis, and convulsions and death in a few minutes: when the dose was not sufficient to kill at once, great anæsthesia and coldness of the skin and also paralysis of the special senses were devel-

* For an account of the hopelessly complicated chemistry of the drug the reader is referred to the 18th edition of the *United States Dispensatory*, whilst a *résumé* of the physiological investigations of the various alleged active principles may be found in the 10th edition of the present treatise. For article upon *sphacelotoxin*, see *Arch. f. Exper. Path.*, 1897, xxxix.

† For cases, see Neubert (*Journ. für Pharmacodynamik*, 1860, ii. 483); also, same case, Richter (*Caspar's Vierteljahrschrift*, xx. 177); Tardieu (*Ann. d'Hyg.*, 1855, i.; *Toledo Med. and Surg. Journ.*, July, 1878).

‡ Davidson reports a case with fluid blood, jaundice, and universal hemorrhages, attributed with doubtful correctness to poisoning by ergot (*London Lancet*, 1882, ii. 596).

oped. In Kersch's[4] experiments intravenous injections of the poison caused marked coldness of the surface and also great muscular rigidity. Upon rabbits, according to Wright, ergot acts very feebly. In birds, as represented by chickens, turkeys, and pigeons, it causes symptoms analogous to those produced in mammals.* Enormous doses of ergot are required to produce toxic symptoms in animals, since in one of Wright's experiments an amount equivalent to two drachms for every pound weight of the dog failed to kill.

An examination of the above summary of the toxic effects of ergot on the lower animals shows that the symptoms are mainly paralytic, and that the only ones which are in any sense characteristic are the anæsthesia and the coldness of the surface. As this coldness of the surface has been noted in various women in whom the drug has caused fatal abortion, it is probably characteristic of the poisoning.

Nervous System.—The action of ergot upon the general nervous system is extremely feeble, but is not well understood: as both Wright and Köhler have found that the voluntary muscles are not affected by the drug, the motor symptoms of the poisoning would appear to be of nervous origin. The statement of Eugene Haudelin,[5] that the peripheral nerves are not affected, has been confirmed by the experiments of Köhler, so far as concerns the motor nerves and the watery extract of the drug. According to Köhler, however, those portions of the drug which are not soluble in water increase the excitability of the efferent nerves, whilst upon the peripheral sensory nerves both the soluble and insoluble preparations of ergot act as feeble depressants.†

Circulation.—According to the observations of Parola, Gibbon, Arnal, Hardy, Beatty (quoted by Stillé), and Bailly and Sée,[6] very large doses of ergot reduce the pulse-rate in man, but only under the rarest circumstances below sixty. Eberty found that in the frog the drug still lessened the rate of the cardiac beats after destruction of the medulla, but that in the atropinized mammal ergot was powerless to alter the cardiac rhythm. By toxic doses the rapidity of the heart's action is increased, and, according to Boreischa, galvanization of the par vagum has at this time little or no effect upon the pulse. It may be that ergot first stimulates and then paralyzes the peripheral pneumogastric, but before any conclusion can be considered established further investigation is imperative.

As was first shown by Charles L. Holmes[7] (confirmed by Köhler and Eberty[8] and by numerous experiments in our own laboratory), a moderate dose of a solution of the watery extract of ergot thrown into the jugular vein of a dog causes a sudden, immediate fall of the arterial pressure, followed almost at once by an enormous and persistent rise of the pressure. The primary fall of pressure is attributed by Holmes to spasm

* See Tessier and Gross, as quoted by Stillé in his work on Therapeutics; also, Bonjean (*Traité de l'Ergot de Seigle*, Paris, 1845).

† In 1884 T. Korkorin, in a St. Petersburg thesis, affirmed that pronounced and characteristic pathological alterations can be found in the spinal cord of animals slowly killed with ergot. The correctness of this, however, seems to be more than doubtful. See paper by A. Grünfeld (*Archiv f. Psych. u. Nerven.*, 1889–90, xxi).

of the pulmonic vessels preventing the interchange of blood between the right and left ventricles, but in view of the facts—that so far as our present knowledge goes ergot does not act locally upon the blood-vessels, that it is a cardiac sedative when in large amounts, and that it does not produce this fall of pressure when introduced gradually into the circulation by hypodermic injection (our own experiments)—it can scarcely be gainsaid that the primary fall of pressure is due to the overwhelming influence of the concentrated ergot as carried directly by the veins to the heart. The influence of minute doses of ergot upon the heart has never been sufficiently studied, but it has been abundantly demonstrated that the large dose depresses the heart-power. According to the early studies of P. Eberty,[9] in the heavily ergotized frog the heart is arrested in diastole, and is unable to respond to stimulation ; whilst in the more recent studies of John C. Hemmeter[10] it was demonstrated that the isolated frog's heart is greatly slowed and still more weakened by the local application of ergot.

The cause of the rise of the arterial pressure is a vaso-motor spasm.* As was first demonstrated by H. C. Wood,[11] division of the spinal cord—that is, separation of the blood-vessels from the vaso-motor centre in the medulla—prevents the ergotic rise of blood-pressure, a fact which has been abundantly corroborated by Hemmeter, who further states that injection of ergot produces plainly visible contraction of the arterioles and capillaries in the omentum of the rabbit when the spinal cord is intact, but is unable to do so after destruction of the cord. Further, Eberty asserts that in the frog after destruction of the medulla ergot is powerless to raise the blood-pressure.

It appears to be an established fact that ergot causes contraction of the blood-vessels and consequent rise of the arterial pressure by stimulating the vaso-motor centre in the medulla. There is at present no sufficient evidence that the drug exerts any direct stimulant influence upon the vessel-walls.

The evidence which has been brought forward in favor of the direct stimulant action of ergot upon the blood-vessel fibres consists of the statements of Holmes, Wernich,[12] and J. H. Peton,[13] that after the nerves going to certain blood-vessels

* The theory that ergot produces a spasm of the blood-vessels was first brought forward by Courhant in 1827. In 1870 Charles L. Holmes found that when the blood-vessels of the frog's web were watched under the microscope and the animal poisoned either with the aqueous extract of ergot or with the powdered drug, the vessels, both venous and arterial, could be seen to undergo a very great contraction. A. Wernich (*Virchow's Archiv*, 1872, lvi. 510) observed that when rabbits in which the arteries of the thigh, back, pia mater, etc., were exposed, received full doses of ergot, these arteries could be seen to undergo a very remarkable diminution in their calibre. These observations have been confirmed by other observers, among whom may be mentioned Vogt, S. Kersch (*loc. cit.*), Max Schüller (*Berliner Klin. Wochenschr.*, 1874, 305), and Boldt (*Schmidt's Jahrbücher*, March, 1872). The latter observer also affirms that there ran through the ergotized capillaries wave-like, peristaltic spasms. Patrick Nicol and J. Mossop (*Brit. and For. Medico-Chir. Rev.*, 1872, I.) have noted with the ophthalmoscope the contraction of the retinal vessels after the exhibition of ergot in man.

have been cut, these vessels can be seen to contract when ergot is injected into the animal, and the fact that in the experiments made by S. Ringer and H. Sainsbury[14] upon tortoises according to the method of Gaskell (see DIGITALIS, page 300), the addition of ergotin greatly slowed the rate of flow through the arterioles. The observations of Holmes, Wernich, and Peton are, however, in distinct contradiction to the very elaborate experiments of Paul Vogt,[15] in which the dilated vessels in the ear of the rabbit whose cervical ganglion had been extirpated could not be made to contract by ergot. Moreover, any observations made with the eye as to the contractions or dilatations of the blood-vessels are of doubtful value.

Greater importance should be attached to the experiments of Ringer and Sainsbury, but in these experiments it was found that the addition of ergotin to the saline solution used had no distinct effect until there was *ten per cent.* of the extract in solution. Ten per cent. of ergotin is enough very seriously to influence the viscidity of the saline solution, and it is probable that the slowing effect of the ergotin was the result of altered physical conditions. Moreover, the effect of such an enormous amount of ergotin upon muscle-fibre is almost certainly paralytic rather than stimulating. Of course, a drug may at the same time stimulate the vaso-motor centres and the muscle-fibres and the walls of the vessels, but there does not seem at present sufficient evidence for the founding of a well-grounded belief that ergot has such double influence.

As has been shown by Haudelin, Boreischa,[16] Brown-Séquard,[17] and others, the toxic dose of ergot produces immediately or after a time a fall of the arterial pressure. The assertion of Brown-Séquard, that this fall of arterial pressure is due, at least in part, to a vaso-motor paralysis, is corroborated by the experiments of Boreischa, who found that when the vessels were paralyzed by section of the spinal cord high up, the fall of pressure produced by the toxic dose of ergot was proportionately not nearly so great as in a normal animal. It is evident that, whilst the therapeutic dose of ergot narrows the blood-paths and increases the arterial pressure by centric stimulation, the large toxic dose lowers the arterial pressure by at the same time depressing the heart and widening out the blood-paths ; the widening out of the blood-paths is probably in part or perhaps altogether due to an action upon the vaso-motor centres, though the influence of ergot upon the heart-muscle would suggest that in toxic dose it depresses the muscle-fibres in the vessels.

Bodily Temperature.—The coldness of the surface in ergotic poisoning seems to depend upon a general fall of temperature. Hemmeter has noticed that this fall of temperature commonly amounts to, and often exceeds, 5° C. in the lower animals and 2° F. in the human being. The cause of it has not been made out. Hemmeter states that in several experiments he has found pronounced reduction of urea elimination in dogs under the influence of ergot, and believes it possible, though not proved, that the fall of temperature is due to diminished general metabolism ; it may, however, be only a secondary phenomenon due to the action of the drug upon the circulation.

Action on the Intestines.—The muscle-fibres in the coats of the blood-vessels are certainly not the only non-striated muscles influenced by ergot. According to Wertheimer and Magnin,[18] ergot produces active movements in the coats of the stomach, and Wright found very active

THERAPEUTICS.—Owing to the power that ergot possesses of intensifying labor-pains, it has long been used in *uterine inertia* during parturition. Indeed, it was for this purpose that the drug was first employed in medicine, and thereby acquired the name of *pulvis parturiens*. The literature of the subject is immense, and all imaginable opinions as to the effects of the drug when given in labor, and as to the advisability of its employment, have been advanced; but, without discussing these, we shall here simply point out the clearly established rules for its use and the clinically determined dangers and advantages of its employment. If ergot be given in very small doses during labor, the natural pains are simply intensified; but if the dose be large enough to have a decided effect, their character is altered: they become not only more severe but much more prolonged than normal, and finally the intervals of relaxation appear to be completely abolished and the intermittent expulsive efforts are changed into one violent, continuous strain. It is evident that, if the resistance be sufficiently great, this may endanger the safety both of the mother and of the child. The dangers to the mother are twofold: there is a possibility of the uterus rupturing itself by its efforts; and, when the head comes down upon the perineum, if the soft parts be rigid there is a very strong probability that they will be lacerated. The danger of uterine rupture is, we think, a remote one; for although several alleged cases have been recorded, yet in very few is the accident clearly traceable to the asserted cause.* The fatal character of the accident is such, however, that the possibility of its occurrence should always prevent the reckless use of the drug.

The improper use of ergot is far more serious in its effects upon the child than upon the mother. During a violent uterine contraction the passage of the blood from the placenta to the child must be interfered with, or, in other words, the respiration of the fœtus is temporarily stopped, so that its life depends upon the aëration of the blood during the intervals. If the latter be very much shortened, the life of the child is greatly imperilled; and if they be abolished, it must be destroyed, unless delivery occurs in a very few moments. These considerations are, we think, sufficient, without further discussion, to show the imperativeness of the rule *never* to give ergot in uterine inertia when there is much *resistance*, either in the bony or in the soft parts of the mother. In primiparæ such resistance is always to be looked for, and its degree often difficult to judge of beforehand; and in such women ergot should not be used for the purposes of expulsion. Even under the most favorable circumstances—when the woman has previously borne children, when the bony pelvis is capacious, and the soft parts are relaxed and dilatable—its use should be entered upon with caution; and if the accoucheur be skilful in the application of instruments, cases must be rare in which the latter are not preferable to the ecbolic.

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* See Stillé (*Therapeutics*, 2d ed., ii. 591).

In women of lax fibre, with roomy pelves, ergot may be used in uterine inertia if instruments are not at hand, or if they are objected to, or if the obstetrician is timid in their application.

At the close of parturition, ergot is very commonly employed to prevent *post-partum hemorrhage;* and in this case there is no objection to its use, and the remedy is invaluable. But, as it requires from fifteen to twenty minutes for its action when given by the mouth, ergot exhibited in this way cannot be relied upon to arrest flooding when it has already set in. To prevent the occurrence of the latter, it is an excellent rule to give a full dose of the ecbolic when the child's head is well down upon the perineum and beginning to emerge at the vulva. After labor, if a tendency to bleeding is manifested, ergot may be administered hypodermically.

For the induction of *premature labor*, ergot has been and still is to some extent used; but it is uncertain in its action, and offers no advantages over instrumental methods.

The success of ergot in arresting hemorrhage after labor soon led to its use in uterine hemorrhages in other than parturient or pregnant women; and the next step beyond this was its employment in other hemorrhages. In all forms of *hemorrhage* in which no direct local application can be made, ergot is to-day probably the most generally used remedy; and even when local applications can be made, ergot may often be exhibited internally as an adjuvant to the local styptic. It is thus employed in *menorrhagia*, *hæmoptysis*, *hemorrhage* from the *gums*, *epistaxis*, etc. Ergot acts with especial rapidity and efficiency in these cases, if given hypodermically. Even when the hemorrhage is apparently dependent upon a dyscrasia, as in *purpura hæmorrhagica*, the hypodermic injection of ergotin may produce the happiest results.* The value of the drug in hemorrhage is no doubt dependent upon its power of contracting the small vessels. In colliquative *night-sweats* due to relaxation of the blood-vessels, ergot is a most efficient remedy.

Allied to its use in hemorrhage is the employment of ergot in *enlargement* of the *spleen* from various causes. Da Costa[20] was the first to suggest hypodermic injections of the drug for this purpose, and he asserts that he has even cured *leukæmia*.

Led by the probably erroneous belief that ergot acts upon the muscle-fibres in the walls of the blood-vessels, Langenbeck[21] injected the drug into the immediate vicinity of the diseased blood-vessels for the cure of *aneurism*, with asserted extraordinary success. The practice has been followed by various surgeons, not only in diseases of the arteries but also for the relief of *varicose veins*. A great deal of local swelling and hardness is induced, involving the blood-vessels themselves, and the good which has been achieved is probably simply the result of the local inflammation, the ergot acting as an irritant and having no specific action.

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* Cases, *Brit. Med. Journ.*, 1874, ii.; *Phila. Med. Times*, v.

Very many years ago F. E. Barlan-Fontayral[22] proposed the use of ergot in *chronic dysentery* and *diarrhœa*, on account of its power of causing contraction of the capillaries; and Massolaz, in an epidemic of chronic diarrhœa among the French troops serving in the East, found that the suggestion was well timed. Although Barlan-Fontayral afterwards published a book* upon the subject, it attracted little or no attention. In 1871 A. Luton,[23] of Rheims, stated, as something new, that he had used ergot with remarkable success in a violent and protracted epidemic of *dysentery*. Successful cases of *chronic diarrhœa* are also reported by other observers,[24] so that trials of the remedy should be made in all obstinate cases.

Another employment of ergot for the purpose of restraining excessive secretion is in *galactorrhœa*, in which affection it has been used with success by Le Gendre,[25] who was led to employ it by an observation of Poyet and Commarmond,[26] that wet-nurses fed upon ergotized bread lost their milk.

The action of ergot upon the blood-vessels suggests its employment in those cases in which there is local or general dilatation of the vessels. We have used it in pulmonic congestion with apparent good results, and it has been highly lauded in the first stages of *pneumonia* by N. S. Davis,[27] by Sunol,[28] and later by other clinicians. It has been especially noted by J. E. Kelly,[29] as giving immediate relief when injected hypodermically in low forms of *pulmonary hyperæmia*, such as occur in typhoid fevers. Ergot has also been recommended by O. Rosenbach, as a means of raising blood-pressure in cases of cardiac disease where there is thought to be insufficient peripheral resistance; and Hemmeter believes that the dicrotic pulse is due to a very low degree of pressure in the arterial system, and is an indication, especially in chronic cardiac disease, for the use of ergot. Rosenbach recommends the drug strongly in aortic insufficiency with cardiac dilatation. Ergot would seem to be indicated as a vaso-motor stimulant in *surgical shock*, but is much less prompt in its influence than atropine. As originally suggested by Brown-Séquard, it is still much used for the relief of chronic *cerebral and spinal congestion*. When there is a rupture of the vessels, as in *apoplexy*, by increasing the blood-pressure it tends to do harm rather than good. It is largely used for the relief of *congestive headaches*, and has been employed in *epilepsy*, in which disease, according to Hemmeter, it greatly increases the efficiency of the bromides. Dehenne[30] states that he has obtained most remarkable effects in the relief of *diabetes* by subcutaneous injections of ergotin. The general clinical experience, however, seems to be that whilst occasionally ergot does great good in diabetes, it usually fails to accomplish anything. When successful, it rapidly diminishes the glycosuria, thirst, and polyuria. In *diabetes insipidus*, though it often fails, ergot is perhaps the most generally useful remedy that we have.

* *Le Seigle ergoté et l'Application de l'Ergotine à la Cure de la Dyssenterie et de la Diarrhée chroniques*, Montpellier, 1858.

In 1872 Hildebrandt[31] announced that in nine cases of *fibroid tumors* of the uterus he had used with the utmost advantage hypodermic injections of ergotin, and this practice has been followed very widely on this continent. It is scarcely to be doubted that cures are sometimes effected; but probably in the majority of cases* the drug simply lessens the uterine congestion, and does good precisely as it does in *chronic subacute metritis* and in *subinvolution* and *hypertrophy* of the *uterus* (Meadows[32]); it may be that sometimes it strangles the growth by causing uterine contractions. If the latter be the case, a cure, as is suggested by Goodell,[33] is to be expected from the remedy only in mural and submucoid tumors.

An objection to the method of Hildebrandt is the great pain and local inflammation which often result; and Goodell proposes as a substitute the use of enemata or suppositories containing the drug.

Toxicology.—Enough has already been said in regard to the acute poisoning by ergot, except it be to state that, when abortion is threatened from its ingestion, in the maintenance of perfect quiet and in the free exhibition of opium are to be found all the measures of relief at our command.

Since the days of Galen there have swept over larger or smaller districts of Europe epidemics of diseases which have been attributed to ergot. In many parts of Europe rye bread forms the great staple article of food of the lower classes. It always contains a small quantity of ergot, but not enough to have any deleterious effect upon the health. When the summer is wet and cold, the rye becomes very extensively ergotized, so that the fungus constitutes a large proportion of the materials entering into the bread. It is under these circumstances that there occur epidemics of *ergotism* or chronic ergotic poisoning. It is not always the rye that causes these frightful losses of life, as Heusinger[34] has traced one epidemic to diseased oats. Before going further, it seems proper to state that Trousseau and Pidoux assert that these epidemics are not dependent upon any specific action of ergot, but are either epidemics of blood diseases or simply the results of improper and insufficient food,—the outcomes of poverty, wretchedness, and famine. It seems to us indisputable that some of the various epidemics which have been recorded were of this character, but certainly it is no less indisputable that others were not. Moreover, numerous scattered cases are on record in which a few persons or a family have been affected with ergotism unmistakably traceable to the use of bread largely composed of the fungus.†

The scope of the present treatise is such as to forbid our entering into an elaborate discussion of the epidemics of ergotism, especially as the subject has no practical bearing so far as the American profession is con-

* See *Amer. Journ. Med. Sci.*, July, 1873; *Amer. Practitioner*, May, 1873, May, 1874, August, 1874; *Clinic*, April, 1873; *Lancet*, May, 1873; *Chicago Med. Journ.*, 1874; and especially Byford's Address (*Trans. Amer. Med. Assoc.*, 1875).

† For an account of a modern epidemic, see *Deutsch. Arch. f. Klin. Med.*, xxxiii. 246.

cerned, since the absence of deep poverty is so complete in our country that no one would feed on largely ergotized bread ; and, in fact, no case of ergotism has as yet been recorded as occurring in the United States.*

There are two varieties of ergotism,—the gangrenous and the spasmodic. In some epidemics the cases have been of mixed type.

Gangrenous ergotism has been especially observed in France, and is believed to be the same as the *Ignis Sacer* or the *Ignis Sancti Antonii* of the Middle Ages, —an affection which in 922 killed forty thousand persons in Southwestern France, and in 1128–29 fourteen thousand in Paris alone. It generally commences with itching and formications in the feet, severe pain in the back, contractions in the muscles, nausea, giddiness, apathy, with abortion in pregnant women, in suckling women drying of the milk, and in maidens amenorrhœa. After some time deep, heavy, aching pains in the limbs, an intense feeling of coldness, with real coldness of the surface, profound apathy, and a sense of utter weariness develop themselves. Then a dark red spot appears on the nose or on one of the extremities ; all sensation is lost in the affected part ; the skin, perhaps over a large surface, assumes a livid red hue, and in the foci of local changes bullæ filled with serum appear. The adynamic symptoms, in severe cases, deepen as the gangrene spreads, until finally death puts an end to the scene. Very generally the appetite and digestion are preserved to the last, and not rarely there is an almost ferocious hunger. The gangrene is generally dry, the parts withering and mummifying ; but sometimes it is moist, and pyæmic symptoms may even be developed. Of course a very large number of cases do not terminate in death ; but the part immediately affected is generally lost. In these cases the toes most generally are the portion destroyed, but it may be any one or all of the extremities ; and the nose, lips, ears, and even the buttocks sometimes bear the brunt of the disorder.

Spasmodic ergotism may in the lightest cases be manifested only by itching, formications, numbness, or complete anæsthesia of the fingers and toes or of the buttocks, and by gastro-intestinal irritation, as shown by colic, vomiting, diarrhœa, or constipation, and withal a ravenous hunger. In more severe cases these manifestations are intensified, and spasmodic symptoms appear, violent and painful tonic contractions affecting especially the flexors of the extremities, interrupted at times by intervals of quiet, but gradually growing into severe general tetanic paroxysms, with opisthotonos and emprosthotonos. In the intervals there are very generally muscular tremblings, and as the case progresses there are developed cerebral manifestations, such as disturbances of vision, photophobia, chromopsia, hemiopia, and periodic amblyopia and amaurosis, giddiness, cataleptic and epileptic paroxysms with or without loss of consciousness, delirium, and idiocy. Gastro-intestinal symptoms are always very marked, but with them are a characteristic ravenous hunger and a longing for sour food and drink. The skin is earthy or yellowish in tint, and is often spotted with boils or pustules or semi-grangenous vesicles. Death is apparently caused by exhaustion ; and in those that recover, various local paralyses, habitual spasms, amaurosis, mental aberrations, or even idiocy often remain through life. In a few cases the symptoms are still more violent, and the spinal and cerebral disturbances soon lead to death.

The primary changes in ergotism are in the blood-vessels. Ergotic gangrene can readily be produced in the comb and tongue of chickens,

* Any one especially interested in the subject will find the literature very well represented in the references of Stillé's work on Therapeutics, Duboué's *Recherches sur les Propriétés Thérapeutiques du Seigle Ergoté*, Paris, 1873, and Husemann's *Handbuch der Toxicologie*.

and Von Recklinghausen asserts that the essential lesion in these cases is hyaline thrombi in the arterioles and capillaries; whilst Grünfeld[35] has found the walls of the vessels thickened, structurally changed, and their lumen occupied by thrombi, in some places full of blood-corpuscles and in other parts undergoing hyaline degeneration.

ADMINISTRATION.—Ergot should not be administered in substance. The wine (VINUM ERGOTÆ—fifteen per cent., U. S.) is very feeble; ecbolic dose, half to two fluidounces (15–60 C.c.). The fluid extract (EXTRACTUM ERGOTÆ FLUIDUM, U. S.) is a very efficient preparation; ecbolic dose, one to two fluidrachms (4–7 C.c.), repeated in twenty minutes, if necessary; in nervous diseases much larger doses are required: thus, in congestion of the spinal cord we usually begin with half an ounce, and increase it to an ounce three times a day.* Extract of ergot (EXTRACTUM ERGOTÆ, U. S.) is preferable to the fluid extract when time is not important, as being less apt to cause nausea. When administered by the mouth, it should be given in capsules containing from five to seven grains (0.3–0.46 Gm.). Its strength is five times that of the fluid extract; when used hypodermically, five grains should be dissolved in five minims of glycerin, fifteen minims of boiled water, and one-fourth of a minim of carbolic acid, and filtered: the danger of causing severe local trouble is lessened by plunging the nozzle of the syringe deeply into the muscular tissues.

Of the so-called *ergotin* two varieties have been proposed, that of Bonjean and that of Wiggers. Bonjean's ergotin is made by exhausting the ergot with water, evaporating to the consistency of a syrup, precipitating the albumin, gum, etc., with an excess of alcohol, decanting the clear liquid, and evaporating to the consistency of a soft extract.

Bonjean's *ergotin* is a refined watery extract, practically the same as the official extract. It is the ergotin of our drug-stores.

The *ergotin* of Wiggers simply contains everything in the ergot which is insoluble in water. Köhler[36] has proved that Wiggers's preparation has no influence upon the circulation, but in toxic doses produces violent convulsions. It ought not to be employed therapeutically.

HYDRASTIS. U.S.

The rhizome and roots of Hydrastis Canadensis, an indigenous perennial, commonly known as *Golden Seal*. Hydrastis contains the alkaloid *berberine*, to which it owes its yellow color, and probably also two other alkaloids, *canadine* † and *xanthopuccine*, besides its characteristic

* It would appear that sometimes, owing to idiosyncrasies, even small amounts of ergot cause much disturbance. Thus, R. B. Faulkner reports (*New York Med. Journ.*, June 14, 1884) a case in which a fluidrachm of the fluid extract caused great sleepiness, swelling and redness of the feet, and violent prickling of the extremities, probably as the outcome of gastric irritation.

† According to the experiments of Bunge, *canadine* in toxic doses produces a brief stage of psychical and motor excitability, followed by general paralysis and depression, with death from respiratory paralysis, and has little direct action upon the blood-pressure. The rate of pulsation in the isolated frog's heart is lessened, but the work done

alkaloid, *hydrastine.** The latter occurs in brilliant four-sided prisms, inodorous and almost tasteless, but having a very bitter and somewhat acrid taste when in the form of a salt. Pure hydrastine and its salts can be obtained in the shops, but the hydrast*in* of commerce is an impure body containing berberine, hydrast*ine*, and probably other more or less active alkaloids besides resin.

PHYSIOLOGICAL ACTION.—According to Falck and Guenste, toxic doses of *berberine* cause in dogs restlessness, convulsive tremblings, thirst, and diarrhœa, and finally partial paralysis of the hind legs. From seven to fifteen grains of it killed rabbits in from eight to forty hours. The symptoms were increased frequency of respiration and tremblings, followed by decrease of the rate of breathing, paresis, paralysis of the hind legs, great dyspnœa, and finally convulsions. Both Schurinow and Curci [37] agree that berberine causes the arterial pressure to fall rapidly from vaso-motor paralysis, Schurinow affirming, however, that late in the poisoning the peripheral vagus is paralyzed, in this being confirmed by Marfori,[38] although Curci asserts that the nerve is not at all affected. The heart's action is at first slowed and afterwards rendered more rapid, the muscular fibres, according to Curci, being finally paralyzed. The respiratory centre is depressed. Abdominal peristalsis is greatly increased. The urine, after toxic doses, becomes albuminous, and sometimes contains epithelial casts, while after death the kidneys are found inflamed (Curci). The action of the drug on the nervous system is feeble, but there is finally loss of voluntary power and of reflex activity, and also of sensation, the anæsthesia being, according to Curci, of central origin, but, according to Schurinow, the result of paralysis of the sensory nerve-trunks. In man, as yet, no violent symptoms have been recorded as produced by berberine. Buchner took nearly twenty grains without causing anything more serious than a loose stool. As a bitter tonic it has been used by various physicians in doses of from two to five grains (0·12–0.3 Gm.), and its action in this dose appears to be that of a simple bitter. It may be given in pill form or dissolved in alcohol.

The dominant alkaloid of hydrastis is *hydrastine*. In toxic doses it causes, in animals, increased, followed after a time by lessened, respiratory movements, salivation, vomiting, excessive peristalsis, muscular tremblings, weakness and rigidity, loss of voluntary movement, rise of bodily temperature (Bunge) (often followed by a fall), feeble, rapid pulse, clonic and tetanic convulsions, increased reflex activity, and death from cramp-asphyxia or general paralysis, or exhaustion with respiratory failure.

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is not decreased by the moderate dose; larger doses paralyze the muscle of the heart. The voluntary muscles are not affected by the alkaloid, nor is the uterus, although diarrhœa with violent intestinal peristalsis is produced.

* For an article on the chemical and physiological activities of a number of derivatives from hydrastine by Falck, see *Virchow's Archiv*, 1895, cxlii.

In a research upon the effect on the lower animals of the long-continued use of hydrastine and hydrastinine, J. De Vos[39] found that these alkaloids have no cumulative action, but that gradually the animals seem to become accustomed to their use. Neither of them in any way disturbed the gastric or intestinal digestion. Albuminuria never occurred, nor was there any apparent disturbance of assimilation.

Nervous System.—We have no knowledge in regard to the action of hydrastine upon the cerebral hemispheres, and so far as we know there have been no cerebral symptoms recorded as produced by it in man. The convulsions which are so prominent in poisoning by it in the lower animals are accompanied by a heightening of reflex activity, and are certainly spinal, since they are not prevented by previous section of the cord, but are stopped by destruction of the cord. This period of motor stimulation is followed in the frog by loss of voluntary movement and depressed reflexes: at first the reflex power can be restored by section of the cord (Cerna[40]), and is therefore probably due to stimulation of Setschenow's centre; later it is irremediable. Cerna believes, but does not prove, that at this time there is centric motor palsy: it may be that this paralysis is really peripheral. In many cases the animal dies in a convulsion before the paralytic stage has been developed. Late in a protracted poisoning, and after death, the motor nerves are depressed or altogether paralyzed (Falck,[41] Cerna), and Bunge[42] has found that the local application of a solution of the alkaloid to a nerve kills it: it would therefore appear that hydrastine is a direct depressant to the motor nerve-trunks. Both Slavatinski (quoted by Bunge) and Mays have noted lessening of the sensibility; Mays[43] found in the frog that the anæsthesia is not prevented in a leg by tying the artery, although the alkaloid when brought in contact with a nerve-trunk paralyzes it. If in Mays's experiments the alkaloid did not reach the peripheral nerves by imbibition or other way, it must act upon both the sensory cord and the sensory nerves: Cerna affirms positively that any action it may have upon sensation is entirely subordinate to its effect upon motion, and Falck states that hydrastine placed in the eye causes no local anæsthesia.

Muscles.—Upon the muscles the alkaloid has some influence, since both Falck and Bunge have found that its not too dilute solution directly applied to a muscle destroys its contractile power, a conclusion which is confirmed by Cerna, who further states that preceding the depression there is a stage of excitation in which the muscular contraction under stimuli is more complete and prolonged than normal.

Respiration.—When death takes place during a convulsion, it probably is due to cramp-asphyxia; but when it occurs during the paralytic stage, it is from paralytic asphyxia (probably, in part at least, of centric origin), the heart-beat continuing after death (Serdzeff[44]).

Circulation.—It is affirmed by Cerna, as the result of numerous experiments, that hydrastine, whether in minute, medium, or toxic doses, and in whatever way administered, always, if in sufficient amount to im-

press the circulation, causes fall of the arterial pressure. This statement, however, is so contrary to the observations of Bartholow,[45] of Fellner,[46] of Falck, of Serdzeff (quoted by Bunge), of Marfori, and of Pellacani, that there must be some error in it. According to the great bulk of authorities, when injected into the vein of an animal hydrastine produces an immediate fall of pressure, followed by a marked rise, which continues for a length of time, unless, indeed, the original dose has been very large, when the pressure falls progressively until death. The first or primary fall of pressure appears to be wanting after subcutaneous injection (Falck), and is probably due to the direct action of the concentrated drug upon the heart. According to Fellner, the rise of arterial pressure is not prevented by previous section of the splanchnic nerve or of the spinal cord high up : if these observations be correct, the rise must be due, at least in part, either to heart stimulation or to action upon the vessels themselves.

It is probable that both voluntary and involuntary muscle-fibres share in the stimulating influence of hydrastine, and that the increase of arterial pressure is caused, first, by direct stimulation of the heart-muscle ; second, by contraction of the muscle-fibres in the smaller blood-vessels. In corroboration of the first of these conclusions we have the remarkably high and full pulse-waves noted by various experimenters, as well as the statement of Serdzeff, that he has proved an actual increase in the working power of the heart, and the observation of Marfori, that a slow, powerful cardiac beat is caused by hydrastine in the isolated heart of the frog. In confirmation of the second conclusion,—namely, that the vessels are contracted,—Marfori found, in experiments made with Roy's oncometer upon the dog's kidney, a constant contraction of the organ. It may be, as Marfori believes, that the vaso-motor centres are also stimulated, but at present this can only be considered a probability. All experimenters agree that after a toxic dose of hydrastine the arterial pressure falls, and that the fall of pressure is in part produced by a direct depresssion of the heart-muscle or its contained ganglia,—a depression which ends in diastolic arrest with loss of muscular irritability. It seems also almost certain that at this period there is a widening out of the blood-paths, due to a direct paralysis of the muscular fibres of the arterioles in vessels, and also of the vaso-motor centres. The characteristic slow pulse produced by the moderate dose of hydrastine, according to Cerna, occurs after section of the pneumogastric nerve, and must therefore be the result of a direct action upon the heart-muscle or its contained ganglia. Cerna states that the vagi nerves retain their power to the end of the poisoning.

Abdominal Action.—It is probable that hydrastine influences both the glands and muscular fibres of the alimentary canal. According to Cerna, it markedly increases the secretion of saliva and of bile, also the intestinal peristalsis.

Uterus.—As long ago as 1883 Schatz called attention to the prac-

tical value of hydrastis in all forms of hemorrhage from the womb, asserting that, though the drug acts well in cases of uterine fibroids or myoma, it is also efficacious in various cases of menorrhagia, dysmenorrhœa, etc. These results have been confirmed by numerous gynæcologists. It is, of course, not possible from these clinical results to determine whether the good is obtained by an action of the drug upon the uterine mucous membrane or blood-vessels or by provoking contractions of the uterine walls. As the result, however, of experiments upon the lower animals, both Fellner and Slavatinski affirm that hydrastine has a distinct ecbolic action, causing uterine contractions in the non-pregnant uterus and abortion in pregnant rabbits. Slavatinski reports a case of premature labor produced by hypodermic injections of two or three grammes repeated daily. It would seem, therefore, that hydrastine is an ecbolic, and that it arrests uterine hemorrhage in part, if not altogether, by provoking muscular contractions.

Eyes.—Hydrastine locally applied to the eye causes at first contraction and afterwards dilatation of the pupil (Cerna).

Absorption and Elimination.—Hydrastine appears to be absorbed from the alimentary canal somewhat slowly; at least it is stated by Bunge that ten times as much of it is required to kill an animal when given by the mouth as when injected hypodermically. Marfori states that it is apt to have a cumulative action when given for a length of time. It escapes unchanged through the kidneys, and has also been found by Hirschhausen in the fæces.

SUMMARY.—By primarily stimulating the spinal motor cord hydrastine causes tetanic convulsions, with heightened reflexes, followed, if the dose have been large enough, by loss of reflex activity, and motor paralysis, which are probably in part due to depression of the motor centres, and are certainly, at least in part, the outcome of depression of the motor nerves and also of the muscles themselves. According to Cerna, the first loss of reflex activity is due to stimulation of Setschenow's centre, and the final muscular depression is preceded by excitation of the muscle-fibres. Death may occur in a convulsion from cramp-asphyxia, or later from simultaneous paralysis of the respiratory centre and of the peripheral apparatus. The arterial pressure is first elevated and secondarily depressed: the first rise of pressure is probably due to the stimulation of the heart-muscle, increasing the output of force, and of both the vaso-motor centres and the muscle-fibres in the arteriole coats, causing contraction of the blood-vessels: the fall of pressure is the result of a direct paralytic action exerted upon the muscle-fibres in the heart and in the arterioles. Hydrastine notably increases intestinal peristalsis, and probably uterine contractions. It would seem to be a universal muscle-poison, which acts upon both striated and non-striated muscle-fibres in heart, arterioles, intestines, uterus, and generally throughout the body; its first stimulant action being followed by marked depression.

THERAPEUTICS.—When locally applied, the preparations of hydrastis have a very remarkable effect upon the mucous membranes. They have been used with asserted excellent results in *chronic gastro-intestinal catarrhs*, especially those due to alcoholic excesses: as Rutherford [47] found

in his experiments upon the lower animals that the hydrastin of commerce caused a marked increase in the biliary secretion, it is probable that in these catarrhs spoken of the good result is, at least in part, due to a specific influence upon the liver and, it may be, other abdominal glands. Nevertheless, it would seem certain that hydrastis has a peculiar action upon mucous membranes. In the second stages of *gonorrhœa*, after the acute inflammation has been subdued, injections of hydrastin, or the fluid extract, suspended in mucilage, are often of service. Five grains of the commercial impure hydrastin, or ten to twenty minims of the fluid extract, may be used to the ounce of fluid. It is also asserted by various specialists that in *otorrhœa*, *nasal*, *vaginal*, and other *mucous catarrhs* the remedy is locally of great value. In *dyspepsia* it has been used as a stomachic stimulant, and has received especial praise in the *vomiting of pregnancy*. At present it is not known to which of the various ingredients of commercial hydrastin these local effects are chiefly due, so that either the hydrastin or a preparation of hydrastis is preferable to the pure alkaloid. These preparations are a tincture (TINCTURA HYDRASTIS—twenty per cent., U. S.), the dose of which is from one to two fluidrachms (4–7 C.c.); a fluid extract (EXTRACTUM HYDRASTIS FLUIDUM, U. S.), dose, from one-half to one fluidrachm (2–4 C.c.); and a glycerite (GLYCERITUM HYDRASTIS, U. S.), dose, from one-half to one fluidrachm (2–4 C.c.). The dose of commercial hydrastin is five to ten grains. For internal or general medication, as contrasted with the local use of hydrastis, the alkaloid or its salts is much preferable to the cruder preparation. As anti-hemorrhagic or ecbolic, a salt of *hydrastine* may be used in doses of one-sixth to one-half grain (0.01–0.03 Gm.). Whenever a speedy action is required, it should be given hypodermically.

HYDRASTININÆ HYDROCHLORAS—HYDRASTININE HYDROCHLORATE. U. S.

Hydrastinine is an artificial alkaloid first produced by Martin Freund by the oxidation of hydrastine. The hydrochlorate is a light yellow crystalline powder, somewhat deliquescent, odorless, having a bitter saline taste, soluble in 0.3 part of water and in three parts of alcohol.

PHYSIOLOGICAL ACTION.—For our knowledge of the physiological action of hydrastinine we are chiefly indebted to Pius Marfori, P. J. Archangelsky, and Kuno von Bunge.[42] No cases of poisoning by the drug in man have been reported, but in frogs the alkaloid is said to produce complete paralysis with death from failure of respiration, the heart being finally arrested in systole; whilst in mammals it causes hyperæsthesia, general tremors, rapid pulse, and dyspnœa, followed by paresis, which is said primarily to affect the front legs and to pass into general paralysis with dilated pupils, lowered temperature, and death from failure of respiration. According to Bunge, intestinal peristalsis is markedly increased by hydrastinine.

Nervous System.—Our present knowledge of the action of hydras-

tinine upon the cerebrum is derived from experiments upon the lower animals, in which it has been found by W. Kiselew[48] that the excitability of the motor cerebral cortex progressively decreases with progressively increasing doses of hydrastinine, although it never entirely disappears; and that the white substance of the brain is affected similarly to but less powerfully than the gray matter. Kiselew has also confirmed the previous observation of Tarchanoff, that the alkaloid arrests or greatly diminishes the convulsive attacks in epileptic guinea-pigs. It is further worthy of remark that Kiselew, in a few cases of human *epilepsy*, obtained very favorable results from the administration of 0.01 to 0.03 gramme of hydrastinine four times a day.

So far as the lower motor apparatus is concerned, the chief symptoms produced by hydrastinine are paralysis with loss of reflex activity, and also lessening of the general sensibility. It seems at present doubtful whether there is or is not an early stage of nervous excitement, since Archangelsky affirms that there is increase of susceptibility to touch and to pain in the frog after small doses, whilst Marfori states that there is no increase of the reflex activity at any time. If there be any stage of excitement, it cannot be well pronounced. It is affirmed that hydrastinine is the natural antagonist of strychnine, and Marfori asserts that the paralysis is of purely central origin. This, however, seems to be incorrect, for not only, as Archangelsky found, is the excitability of the voluntary muscle lessened by the toxic dose of the alkaloid, but Bunge has shown that both the peripheral nerves and the muscle-fibres were paralyzed by a local application of the hydrastinine solution.

In the advanced poisoning the respiratory centre seems to show the depressing influence of the alkaloid, and hence respiratory failure; but here again, according to Archangelsky, especially when the dose has not been too large, there is a period of primary centric stimulation.

Circulation.—The elaborate studies of Bunge show that hydrastinine has no influence upon the blood itself, but all observers are in accord in stating that the blood-pressure is increased by the large dose of the alkaloid. The increase appears to be in part of cardiac and in part of vascular origin. Thus, both Marfori and Bunge, in experiments made with the Williams apparatus, found that the systolic impulse of the isolated frog's heart becomes abnormally strong under the influence of the drug, and that the amount of the heart's work is distinctly increased. A second cause of the rise of the arterial pressure is asserted to be contraction of the vessels, which, according to Marfori, may become so great as entirely to arrest the renal secretion. As the result of elaborate experiments made with section of the splanchnics and of the spinal cord, Archangelsky reaches the conclusion that the contraction of the vessels is chiefly of peripheral origin,* although there is at the same time

* The assertion of Bunge, that because in heavily chloralized animals hydrastinine fails to elevate the pressure, therefore it acts chiefly upon the vaso-motor centre, is a non

some stimulation of the vaso-motor centres in the medulla,—a conclusion concordant with Marfori's results. When the amount of the hydrastinine has not been too large, the elevated arterial pressure gradually returns to the normal (Bunge); but after a fatal dose of the alkaloid a pronounced fall of pressure finally comes on, apparently as the result of the paralysis of progressive asphyxia, since artificial respiration will bring back the pressure to the normal (Marfori): further, it is asserted by various observers that the heart is finally arrested in systole, so that it would seem that hydrastinine differs from hydrastine in not being a cardiac paralyzant in any dose.

Pupils.—Archangelsky has noted that one to two drops of the ten per cent. solution of a salt of hydrastinine in the eye will produce a dilatation of the pupil, which reaches its maximum in two to three hours, and remains twelve to fifteen hours.

Uterus.—The effect of hydrastinine upon the uterus was studied in pregnant and puerperal dogs, cats, and rats by Archangelsky, who found that it produced rhythmic contractions, independent of any vaso-motor influences, apparently by stimulation of the uterine walls. On the other hand, Bunge, having failed in two experiments to provoke abortion or uterine contractions in pregnant animals by large or even fatal doses of the alkaloid, affirms that it is not an ecbolic. Nevertheless, Faber,[49] as the result of a number of trials, states that hydrastinine given hypodermically during human labor very notably increases the force and length of the uterine contractions, causing a spasm which affects all portions of the uterus, and which is similar in character to that provoked by ergot. In some of the cases there was uterine tetanus, lasting as long as fifteen minutes. Faber also asserts that distinct contractions can be produced in the unimpregnated womb.

Absorption.—Bunge has found that hydrastinine is readily absorbed and eliminated unchanged, chiefly with the urine, but also to some extent with the saliva, bile, and intestinal secretions. It did not appear to increase the amount of bile secreted.

SUMMARY.—Hydrastinine in sufficient dose appears to be a powerful depressant to the whole motor tract, commencing in the motor area of the cerebral cortex and ending in the muscle,—motor brain, motor cord, motor nerve, and muscle being all more or less affected. Whether this depression be or be not everywhere preceded by a brief stage of excitement is at present somewhat uncertain, but it is extremely probable that there is a primary stimulation, at least, of the muscles. It is a stimulant to the circulation; the heart under its influence acts more slowly, but more powerfully, and is in fatal poisoning finally arrested in systole, whilst the blood-vessels undergo powerful contractions until late in the poisoning; the vascular contractions are probably the result of stimulation both of the vaso-

sequitur, as chloral acts upon the whole circulatory apparatus. Moreover, Bunge's own experiments show that the alkaloid lessens the size of the spleen by contracting the blood-vessels.

motor centres and of the muscle in the walls of the arterioles. The final fall of arterial pressure is asserted to be the result of the asphyxia, and not produced directly by the drug. Although it is denied by some, hydrastinine appears to be a powerful oxytocic, and it is probable that its action upon the heart, the arterioles, the uterus, the intestines, and the skeletal muscles is the outcome of a wide-spread general muscular stimulation.

THERAPEUTICS.—Hydrastinine is used in medicine chiefly for those complaints for which it was originally recommended by Falck,—namely, *menorrhagia*, *metrorrhagia*, congestive *dysmenorrhœa*, and even *endometritis*. The testimony in favor of its arresting uterine hemorrhage in all forms is, on the whole, very consistent, and is abundant, but it is also believed by many gynæcologists to have some alterative influence upon the mucous membrane of the uterus. It is affirmed by some gynæcologists, but denied by others, that it is an active oxytocic, and exerts its influence upon impregnated and unimpregnated wombs largely by causing muscular contractions. It will be seen that the range of its usefulness in gynæcology is entirely similar to that of hydrastine ; it has, however, acquired popular favor more rapidly and decidedly than the natural alkaloid. It may possibly be more effective as an ecbolic, but its superiority probably lies in chief part in its being distinctly less toxic and producing cardiac stimulation rather than cardiac depression. When an immediate impression is desired, the sulphate should be given hypodermically. When a prolonged continuous action is required, it may be administered by the mouth. The results obtained by Kiselew demand a fair trial of it in *epilepsy*. Hydrastinine has some value as a subsidiary cardiac tonic ; it does not belong in the same class as digitalis, but its tonic influence is often decidedly helped by its cardiac action. Dose, three-quarters of a grain to a grain and a half (0.05–0.1 Gm.).

GOSSYPII RADICIS CORTEX. U. S.—The root of the ordinary cotton-plant, the Gossypium herbaceum, is said to be used by the negroes in various portions of the South as an *abortifacient*, and Bouchelle, as long ago as 1841, affirmed that it has medical properties similar to those of ergot. It has not, however, come into general use, and our knowledge of its properties is very scanty and uncertain. In the experiments of I. C. Martin[50] enormous doses produced heaviness and stupor in both frogs and mammals, but did not cause abortion in pregnant guinea-pigs and rabbits : neither the spinal cord, the muscles, nor the nerves were affected ; but H. I. Garrigues[51] has found it a most serviceable agent in arresting hemorrhage and ameliorating the other symptoms in *uterine* polypoid and fibroid *tumors*, and even in *uterine cancer*. He insists that the commercial fluid extract is inert and the decoction must be freshly prepared. The oxytocic dose of a decoction (four ounces in a quart of water boiled to a pint) is stated to be a wine-glassful, to be repeated every thirty minutes as necessary. The remedy has also been employed in *amenorrhœa* and in *dysmenorrhœa*, in which

diseases from three to five grains of a solid aqueous extract have been given three times a day. The fluid extract (EXTRACTUM GOSSYPII RADICIS FLUIDUM, U. S.) may be used in doses of a fluidrachm (3.7 C.c.)

The *Smut of Indian Corn* (*Ustilago*) appears to have active medicinal properties, and should be investigated. It has been used with alleged success in *uterine inertia* during labor by Dujardin-Beaumetz.[52] James Mitchell[53] has found that in the frog the ustilago maydis abolishes sensation and reflex action before voluntary motion; he states that reflex action is destroyed at a time when motor nerves and muscles are still active, and that consequently the first influence of the poison is upon the sensory side of the lower nervous system; late in the poisoning the whole motor tract became involved. According to W. A. N. Dorland, in doses of one to two drachms of the fluid extract, it has a very marked influence upon the uterine pains in labor, increasing their severity, frequency, and duration. He asserts that it will not produce a prolonged tonic contraction as does ergot.*

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FAMILY IX.—COUNTER-IRRITANTS.

Counter-irritation.—Almost from time immemorial physicians have believed that morbid processes in deep-seated or superficial organs could be modified by irritations artificially induced in distant parts. To the drugs used for producing these remedial irritations the name of revulsives, or counter-irritants, has been given, the process being called revulsion, or counter-irritation.

The question as to the manner in which a counter-irritant acts is essentially distinct from the question whether it does or does not act. However crude and uncertain our theories may be, clinical experience has demonstrated the value of counter-irritants in various internal conditions. It is proved beyond cavil that internal morbid processes may at times be relieved by creating external irritations.

Our present explanations of the way in which counter-irritants act are certainly not satisfactory. There are abundant physiological proofs demonstrating the connection between distant organs having no apparent anatomical connection; such is the relation between the mammary glands and the uterus; such are the phenomena of so-called metastasis seen in mumps, gout, and other constitutional disorders, in which the development of a new irritation is accompanied by the disappearance of one already existing. Familiar examples, also, may be found in the paraplegias sometimes produced by irritation of a renal calculus, in the headache of gastric irritation, in the shoulder-pain of diseased liver, and in the amaurosis or epileptiform attacks sometimes caused by a decayed tooth. In the well-known experiment of Brown-Séquard it was found that if one sciatic nerve of the guinea-pig be cut epileptic attacks may be produced by gently rubbing the back of the ear upon the same side.

One commonly offered explanation of counter-irritation is that there is only a certain amount of blood and of nervous energy in the body, and that if the blood or the nervous energy be drawn to one part there must be less in another part. Surely, however, the amount of blood drawn to the skin by a mustard plaster is too small sensibly to affect the general mass in the body. It is more probable that the phenomena of counter-irritation are the result of reflex disturbances of the vaso-motor nerves which influence the size of the blood-vessels, or of the trophic nerves which directly affect nutrition.

It is of great practical importance to know where the counter-irritant should be placed to affect most powerfully any given internal organ.

We have no thoroughly scientific experimental knowledge as to this matter, but it has been clinically demonstrated that the general law for deep-seated parts is that the revulsant should be put directly over the part. When a superficial action is desired, other directions are needed. We are indebted to Anstie for pointing out what appears to be a law, or at least a good working rule for practice,—namely, that when a superficial part supplied by the anterior branches of a spinal nerve is to be affected, the counter-irritant should be placed over the posterior roots of the nerve. Not only can obstinate neuralgia often be relieved by this reflex action, but also the inflammatory changes so often coincident with intercostal neuralgia. The law seems also to apply to cervical nerves, since the proper position for the blister in trigeminal neuralgia is back of the ear or on the nape of the neck.*

For the purposes of study, counter-irritants are conveniently arranged under two heads: first, those which do not provoke decided alterations of the dermal structure, but simply cause an irritation which soon passes away; these are the RUBEFACIENTS: second, counter-irritants which produce severe structural alterations; in this class belong the hot iron, the issue, the seton, and other destructive appliances, and also the epispastics, vesicatories, or more colloquially blisters, which are used to produce that peculiar inflammation of the cuticle with an outpouring of serum commonly known as the blister.

In choosing between a rubefacient and a blister, the physician is guided by the character of the disease present in the subject. A rubefacient causes a wide-spread, intense but temporary, irritation and congestion of the part,—an irritation which for the moment produces a strong influence, but leaves no permanent impression upon the nutritive acts of the diseased organ. A rubefacient is to be employed when the disease is functional,—when there is only a nervous disturbance or a congestion to be dealt with; whereas the blister is useful when inflammation has produced permanent change. Very frequently in inflammatory conditions, however, rubefacients are useful to relieve accompanying congestion. Thus, in a pneumonia the rubefacient may have no effect upon the focus of the disease, but may be very serviceable in checking a wide-spread collateral congestion.

To the careful use of rubefacients there are scarcely any *contra-indications;* some caution is, however, necessary in their application. A severe internal irritation may so successfully counter-irritate against the external counter-irritation that the latter has for the time being no apparent effect, and yet really exerts a disorganizing influence. Thus, a mustard plaster, under the circumstances named, may at the time of its application produce no pain or redness, and yet twenty-four hours after-

* The statement of A. Dumontpallier (*Gaz. Hebdomadaire*, November, 1879), that the best results of counter-irritation are obtained by applying the counter-irritant upon the opposite side of the body, so as to be exactly symmetrical with the diseased part, has never to our knowledge been confirmed.

wards disorganizing inflammation may set in at the seat of the application. When there is severe internal irritation the counter-irritant should always be removed when it has been applied long enough to endanger violent local effects, even though it has exerted no sensible influence.

There is one use of rubefacients which is not that of counter-irritation, but which is often of practical importance. An irritation of the sensitive nerve in the normal animal produces an immediate vaso-motor spasm, and in certain conditions of the body irritation of the mucous membrane or of the skin is of great service in stimulating respiration or circulation. In a true exhaustion rubefacients are of very little value, for the only possible source of absolute increase of power to the system is in food; and in exhaustion those stimulants should be employed which increase the power of assimilating food. For this reason, external irritants are useful as stimulants in conditions of depression rather than of exhaustion. Especially are they valuable when there is wide-spread loss of functional activity in the vaso-motor system. Such conditions of depression, with vaso-motor weakness, exist in *acute collapse* from any cause, in *shock* following injuries, in the first stage of *pernicious malarial fever*, and in other cases when the powers of the system are seemingly overwhelmed by some depressing agency.

Blisters are especially useful in inflammations of serous membranes, such as *pleuritis* and *peritonitis;* are very strongly recommended by some practitioners in parenchymatous inflammations, such as *pneumonia;* and may be of service in persistent forms of nervous irritation, such as the *maniacal delirium* of fevers, when dependent upon the irritant action of a blood-poison, and not upon exhaustion. The amount of serum which is poured out from a blister is sometimes quite large, and vesicants have even been employed to relieve *dropsy*. In general dropsy their use is simply unjustifiable; but in *local dropsies*, as, for example, serous effusion into the pleural sac or into the pericardium, dependent upon local inflammation, they often do good, not only by affecting favorably the disease-process, but also by hastening the removal of the effusion.

In some chronic affections, long-continued severe counter-irritation is required: in such cases a blister may be "kept open" by the use of stimulating ointments, such as the mezereon ointment. In *chronic inflammation* of the *joints*, repeated blistering is very often of service. When the inflammatory action is rheumatic, in our experience better results are obtained by repeated blistering than by keeping a blister sore by means of irritants. In *neuritis*, whether rheumatic or otherwise, blisters are often of service: they should be applied as a long narrow strip along the course of the nerve. In obstinate local *neuralgia*, very mild blistering over the seat of pain, or in accordance with Anstie's law, is sometimes advantageous.

The *contra-indications* to the use of blisters are high arterial and febrile excitement and a decided want of vital power. In the former case, the irritating influence which they exert upon the general system

may increase the constitutional disturbance to such an extent as to do more injury than any local benefit derived from them can do good. When the vitality is very low, blisters may give rise to sloughing ulcers, which, refusing to heal, may waste very seriously the already exhausted system. Hence, in all acute diseases of such type that the nutritive forces are exceedingly depressed, blisters must be avoided, or be used only with great caution. For the same reason, great care must be exercised in their employment in the very young or the very aged. Very rarely indeed is a blister called for in the case of a young infant, and if it be employed at all, it should be allowed to remain in contact with the skin only long enough to produce slight pain or redness, and the complete vesication should be obtained by the after-use of a poultice.

The hot iron or other *destructive counter-irritant* is to be used only in cases of continuing chronic disease with structural lesion. At present, neither the moxa nor the issue is ever employed in civilized countries; the seton with extreme rareness. The actual cautery, however, affords a valuable method of treating *chronic neuritis*, *chronic meningitis*, cerebral or spinal, and various forms of *chronic arthritis*.

EPISPASTICS.

There are various substances which are capable of producing vesication, but the only one in ordinary use is cantharides. In cases of emergency ammonia is sometimes employed. (See page 758.)

CANTHARIS—CANTHARIDES. U.S.

The dried bodies of the Cantharis vesicatoria, a beetle inhabiting Southern Europe. *Spanish flies* are from half an inch to nearly an inch in length and two to three lines in breadth, and have a large heart-shaped head and brilliant metallic-green elytra, or wing-cases. Their odor during life is very strong and fetid, but is almost entirely lost in drying; their taste is urinous, very burning, and acrid. When ground, Spanish flies afford a grayish-brown powder, full of minute greenish spangles, the remains of the feet, head, and wing-cases. The active principle of cantharides is *Cantharidin*, which occurs in white crystalline scales, is inodorous, tasteless, insoluble in water, nearly so in cold alcohol; soluble in ether, benzole, the oils, and very freely so in chloroform. Notwithstanding the insolubility of pure cantharidin, Spanish flies yield their virtues to alcohol and to water.

Local Action.—Absorption and Elimination.—Cantharides is very irritating, and, when applied to the skin, causes at first redness, with burning, then free vesication and severe pain, and, if the contact be longer maintained, deep inflammation and sloughing. Upon the mucous membranes it produces a no less intense effect. The cantharidin is rapidly absorbed, and is eliminated unchanged by the kidneys.

General Action.—The first symptom produced by the small dose of

cantharides is burning in the genito-urinary passages. After the ingestion of ten minims of the tincture the irritation may amount to complete strangury. The toxic dose produces in a very few minutes burning in the pharynx and œsophagus and a sense of stricture in the throat. The pain soon spreads to the stomach, and vomiting comes on. The symptoms rapidly increase in severity; the abdominal pain becomes very severe, and in the majority of cases purging takes place. The matters rejected by the stomach are first mucous (with, if the drug have been taken in powder, little greenish specks through them), then bilious, and finally bloody. The stools are mucous, then fibrinous, bloody, becoming often very scanty, but excessively numerous, and in their passage accompanied by great tenesmus. Probably in most cases, early in the poisoning severe salivation is developed, and is frequently accompanied by great swelling of the salivary glands. Sometimes death occurs in a very short time, from collapse produced by the intense gastro-intestinal inflammation; but more generally it is postponed for some hours, and a new train of symptoms arises. Aching pains in the back and very frequent micturition indicate the commencing urino-genital irritation. These symptoms increase in intensity until there is a constant, irresistible desire to urinate, with violent tenesmus of the bladder, and yet an inability to pass more than a few drops of urine, which is albuminous, and not rarely bloody. In some cases there is a violent erotic excitement, an unquenchable lust, accompanied in man by numerous seminal emissions;* violent priapism, swelling and heat of the organs, and even severe inflammation of the parts may indicate the intensity of the local action of the poison; sometimes gangrene ultimately occurs. Consciousness and general power are often long preserved when the local symptoms and agony are intense, but, if the dose have been large enough, sooner or later collapse comes on, with the usual accompaniments, and the prostration deepens into complete powerlessness, stupor, coma, and finally death. In some cases violent hydrophobic delirium and severe tetanic convulsions are said to have occurred (Tardieu). Paraplegia has been noticed in several cases by Pallé:[1] it was probably reflex in its origin, and due to the intense irritation of the genito-urinary organs.

In animals, cantharides produces very much the same symptoms as it does in man. In dogs, according to the experiments of Orfila and of Beaupoil, the symptoms of gastro-intestinal inflammation are more prominent than those of irritation of the genito-urinary tract. It has been asserted that the lack of erotic excitement in these cases shows that the medicine acts differently upon man and upon animals. As already stated, however, erotic delirium is very often absent in fatal poisoning in man, while Schroff states that ten drops of the tincture of cantharides will frequently produce great sexual excitement in man, and the whole drift of the evidence is that libidinous desires are much more apt to be caused by amounts of Spanish flies but slightly toxic than by fatal doses. Indeed, the irritation caused by the latter would seem to be too intense, the general perturbation too great, for

* Cases, *Journ. de Pharm. et de Chimie*, June, 1871.

erotism to be induced. There appear to be the same differences in the effects of different doses of the drug upon animals. Fatal doses very generally do not excite sexual desire; but Schubarth (quoted by Stillé) found that small doses do cause evident salaciousness and irritation of the genital organs, while, according to Husemann,[2] the peasants of Northern Germany habitually give cantharides to cows when backward in coming into heat at the proper season.

According to Cautieri,[3] toxic doses of cantharides rapidly lessen blood-pressure and the force of the cardiac pulsations, but markedly increase the pulse-rate. Cautieri found in animals killed with cantharides marked hyperæmia of the brain and spinal cord, and nephritis: Galippe[4] noted inflammation of the alimentary canal, kidneys, and bladder.

THERAPEUTICS.—Cantharides is employed internally only for the purpose of influencing the genito-urinary organs.* When cantharides is freely used externally as a vesicant there is always some danger of the absorption of a sufficient amount of the active principle for strangury to be induced. The blister should therefore not be left on longer than is absolutely necessary, and in susceptible persons care has to be exercised in its use: whenever active irritation of the kidneys exists, cantharidal blisters should not be applied.†

TOXICOLOGY.—The minimum fatal dose of cantharides is not certainly determined, and probably varies very much. According to Stillé, twenty-four grains of the powder, taken in two doses, have caused fatal abortion, and an ounce of the tincture has destroyed life after the lapse of a fortnight. After death, intense injection, swelling, patches of exudation, loss of epithelium, and other results of inflammation are found along the whole tract of the alimentary canal; intense hyperæmia of the kidneys, with contraction and congestion of the bladder, also usually exists. According to the experiments of Aufrecht,[5] all the forms of nephritis may be produced by cantharidin, but it is probable that in most cases of poisoning the first change is exudation of the white blood-corpuscles, rapidly followed by a desquamative nephritis, with profound alteration in the glomerules (see Ida Eliaschoff[6]).

There is no known antidote to cantharides, and the treatment of the poisoning must be conducted upon general principles. The stomach should be washed out repeatedly and freely by large draughts of warm water, aided by the stomach-pump or tube, or by a stimulating emetic if the stomach-pump be not at hand. Large quantities of mucilaginous or albuminous drinks should be taken; and all oily substances should be avoided, as favoring the solution, and consequently the absorption, of the poison. Opium should be freely exhibited, especially by the rectum, to allay pain and relieve the strangury. For the latter purpose warm sitz-

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* See DIURETICS and EMMENAGOGUES.

† In 1891 Liebreich advocated the use of cantharidin salts in *lupus*, *phthisis*, and other forms of tubercular disease. His theory of their action was, however, very improbable, and the method has so entirely failed in practice that it is not necessary here to do more than refer the curious reader to the tenth edition of this treatise for information concerning it.

baths or general baths should be employed. In some cases leeches to the epigastrium are advisable. When the suffering is very intense, the cautious use of anæsthetics is not only justifiable, but imperative.

ADMINISTRATION.—For blistering, the *Cantharides Cerate* (CERATUM CANTHARIDIS, U. S.) is best spread upon sticking-plaster in such a way as to leave a margin about an inch in width, which shall adhere to the skin and hold the plaster in its place. In order for a blister to "draw" thoroughly, it usually has to be left on some eight hours; but in most cases the same result can be achieved with less suffering by allowing the blister to remain only five or six hours, or until decided redness and slight vesication have been induced, and then applying a flaxseed poultice. In certain localities vesication requires a much longer application than that just spoken of; thus, upon the shaved scalp a blister will rarely act efficiently in less than twelve hours, and often not in that time. In maniacs, in the delirious sick, in children, and in other unruly patients it is often necessary to put on a blister in such a way that the sick person has no control over it. For this purpose the *Cantharidal Collodion* (COLLODIUM CANTHARIDATUM—sixty per cent., U. S.)* may be used. It is ordinary collodion impregnated with cantharidin, and on evaporation leaves an adhesive blistering film: two or three coats of it should be applied by means of a camel's-hair brush. When there is any especial danger to be feared from absorption of the active principle, the use of the poultice, after a brief application of the blister as described above, should always be practised. The tincture (TINCTURA CANTHARIDIS—five per cent., U. S.) is used internally in doses of three to five drops (0.18–0.3 C.c.).

RUBEFACIENTS.

SINAPIS ALBA—WHITE MUSTARD. U.S.
SINAPIS NIGRA—BLACK MUSTARD. U.S.

The seeds of Brassica alba and Brassica nigra respectively,—European crucifers, cultivated in the temperate regions of the world. These seeds are minute, globular bodies, yellowish within: they are to be distinguished one from the other by the smaller size, external brown color, and more fiery taste of the black mustard, and the light yellowish exterior of the white mustard.

Black Mustard yields on distillation a *volatile oil*, which does not pre-exist in the seeds, but is formed by the decomposition of *sinigrin* or *potassium myronate* in the presence of emulsin. OLEUM SINAPIS VOLATILE, U. S., is a colorless or yellowish fluid, of an intensely pungent, or corrosive, odor and taste. A momentary contact with it suffices to redden and blister the skin, and mucous membranes are said to be rapidly destroyed by its vapors.

White Mustard contains *sinalbin*, which in the presence of water and

* A case of poisoning by cantharidal collodion, see *Phila. Med. Times*, iv. 312.

emulsin forms *acrinyl sulphocyanate*, an oily, non-volatile, very acrid substance, upon which the activity of white mustard depends.

THERAPEUTICS.—Mustard affords a most excellent material for the practice of mild revulsion. One advantage it possesses is the ease with which it can be controlled, all grades of action, from the mildest impression up to severe blistering, being at the will of the practitioner. It should be remembered, however, that the blister produced by it discharges but little, and is exceedingly sore and painful, as well as very slow and difficult of healing: so that, as an epispastic, mustard is in every way inferior to cantharides, and should not be employed. The black mustard is much stronger than the white, and must usually be diluted at least one-half (by the addition of flour or of flaxseed meal). The white variety may sometimes be employed pure, but generally it also should be reduced in strength.

In many cases it is desirable to maintain for hours a mild, equable counter-irritant impression, and this may be done by adding from one to three teaspoonfuls of mustard, more or less, to a poultice of flaxseed. A mustard poultice (half-and-half black mustard, three parts to one of white mustard and flour) may generally be left on from twenty minutes to half an hour without danger of blistering. Weaker preparations may be used longer.

A mustard plaster may be prepared like an ordinary poultice; but a very convenient method is to take a newspaper folded to a little larger than the desired size, and tear open the front piece so that it can be folded back like a flap, leaving one edge attached; next, to spread upon the thick portion the mustard, leaving the edges free, and then to close the flap upon it and fold the edges back to the desired shape: when done with, this plaster can be thrown away, and no rags are lost. The mustard draws well through the single layer of newspaper covering it, but is, we think, less apt to leave troublesome after-soreness than when employed in the usual manner.

CHARTA SINAPIS, U. S., or *Mustard Paper*, consists of black mustard mixed with solution of gutta-percha and spread upon stiff paper four inches square. It is not so good as the domestic plaster, because not so easily regulated as to power and size.

CAPSICUM and the *stronger spices* afford excellent materials for rubefaction. Cayenne pepper is nearly as strong as mustard, but is much less pleasant to handle, on account of the readiness with which it is diffused, and is much less frequently employed. *Spice-plasters* are useful when it is desired to make a steady, continuous mild impression, as in certain abdominal complaints.

Spice-plasters may be made by the apothecary by means of the following recipe. Take of powdered ginger, ℥ii; powdered cloves and cinnamon, each, ℥i; Cayenne pepper, ʒii; tincture of ginger, f℥ss; honey, q. s.; mix the powders, add the tincture, and sufficient honey to make of proper consistence for a stiff cataplasm. The

domestic spice-plasters are much more elegant and cleanly than those made on the above plan. They are to be prepared as follows. Take equal parts of ground ginger, cloves, cinnamon, and allspice, and one-fourth part of Cayenne pepper, and thoroughly mix them; then put the resulting dry powder into a previously prepared flannel bag of the desired size, distribute the powder equably through the latter, and quilt it in,—*i.e.*, run lines of stitching across the bag, so as to confine the powder in little compartments: when using, moisten thoroughly with common whiskey or with alcohol. A plan which has seemed to us still more pleasant is to put two ounces of *unground* ginger, an ounce of unground cloves, cinnamon, and chillies, or African peppers, in a pint bottle, and pour the whiskey upon them. After this has stood awhile, the liquor is to be put upon a piece of flannel of the proper size, and the latter is to be laid upon the part and covered with a larger piece of oiled silk, or else a piece of spongiopilin may be employed. If the strength of the preparation is too great, it can readily be reduced by dilution; if it is too little, it can as readily be increased by adding more of the spices, especially of the peppers. In many cases, when the tenderness is very great, the weight of the spice-plaster is objected to. Under these circumstances the substitute here proposed is especially valuable.

Oil of Turpentine is a very powerful rubefacient, capable, if applied to the skin for too long a time, of destroying the epidermis. It produces, when properly used, simply an intense diffused redness. The most frequent mode of application is in the form of *stupes*, which should be made by dipping a piece of flannel, previously wrung out with warm water, into a cup of turpentine which has been warmed by setting it in hot water, and then wringing out all excess of the turpentine and applying. These stupes may be left on from ten to thirty minutes, according to the severity of the impression desired and the susceptibility of the patient's skin. On some persons the least contact of turpentine, or even of its vapors, produces a most painful furuncular eruption. Where this idiosyncrasy exists, of course the remedy should never be used. The official liniment (Linimentum Terebinthinæ, U. S., *Kentish Ointment*) has been used as a stimulant application to *burns* and old ulcers, but has passed out of vogue.

Ammonia is a most efficient rubefacient, which in its general relations has been sufficiently discussed elsewhere. When great haste is required, it may be employed as an epispastic by applying a piece of common lint saturated with the stronger water of ammonia, and covering it with some impervious coating. Great care must be practised lest the ammonia act as an escharotic, since a too prolonged application may produce a deep slough. To raise a blister requires from five to ten minutes. On account of its cheapness and efficiency, ammonia is very largely used in extemporaneous liniments. In prescribing, it must always be borne in mind that there are two waters of ammonia,—Aqua Ammoniæ Fortior, U. S., with a specific gravity of 0.90, containing twenty-eight per cent. by weight of the gas, and Aqua Ammoniæ, U. S., with a specific gravity of 0.960, containing ten per cent. by weight of the gas. The rubefacient action of ammonia is less permanent than that of turpentine.

The liniment (LINIMENTUM AMMONIÆ, U. S.) is composed of three hundred and fifty parts of ammonia water, fifty parts of alcohol, and six hundred parts of cotton-seed oil.

PIX BURGUNDICA, U. S., or *Burgundy Pitch*, is a concrete juice obtained by wounding the Abies excelsa, or Norway spruce,—lofty forest trees of Middle and Northern Europe,—melting the product of the exudation with hot water, and straining. It is hard, opaque, brittle, of a feeble terebinthinate odor and taste, and contains resin and a minute amount of volatile oil. It is a mild rubefacient, which, in the form of plaster, may be kept applied for a long time in *chronic bronchitis* and in *rheumatic affections* of the trunkal muscles. The official plaster (EMPLASTRUM PICIS BURGUNDICÆ, U. S.) contains fifteen per cent. of wax. The *Warming Plaster* (EMPLASTRUM PICIS CANTHARIDATUM, U. S.) contains one part of cantharides cerate to twelve parts of Burgundy pitch, and is a very decided counter-irritant, whose prolonged use will sometimes blister.

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FAMILY X.—ESCHAROTICS.

ESCHAROTICS are drugs which are used to destroy diseased or sound tissue. Many of them exert a purely chemical influence, while others seem to destroy life by directly affecting the vitality of the part, and are said to act dynamically. Those which act chemically do so in several ways: some, like bromine, probably produce an intense corrosive oxidation, while others, like sulphuric acid, abstract the water.

Escharotics are used for various purposes. Formerly they were employed to open abscesses; but in the very few cases in which the knife is not allowable, aspiration usually affords a superior and safer method. They are constantly applied to destroy unsound, harmful tissues and growths. Thus, they are used to remove the specific tissue of a *chancre*, or to kill a *malignant* or *semi-malignant tumor*. Another purpose which they fulfil is the destruction of *poisoned wounds*. In these cases they may in some instances destroy the poison itself, but at other times they simply prevent the absorption of the toxic agent by putting an end to the life-actions of the tissue containing it. It is hardly necessary to mention all the various cases in which caustics are employed to overcome the effects of poisoned wounds. *Hydrophobia* is a perfectly uncontrollable disease; but the thorough destruction of the wounded tissue at any time before the manifestation of the symptoms will probably prevent its occurrence, as it certainly will if performed early. In *malignant pustule*, life depends upon the free early use of escharotics. Escharotics are employed to produce ulcerations which shall be the bases of *issues;* also, by destroying the exuberant granulations or the indolent surfaces of *ulcers*, to remove at the same time diseased tissue, afford protection to the parts below by forming an impermeable surface, and exert such alterative action upon the part as shall modify for good the life-processes.

It is evident that the choice of the caustic should depend upon the object to be attained. When large tumors are to be killed, or when it is all-important completely to destroy a poisoned wound, a powerful deep-reaching escharotic must be employed; but when the surface of an ulcer is to be filmed over, a caustic which acts superficially and forms a dense albuminous coating, as does silver nitrate, is to be chosen.

An observation of N. A. Randolph and S. G. Dixon[1] indicates that the pain produced by a caustic may be almost nullified by the use of

cocaine. They find that the saturated solution of cocaine in nitric acid acts as powerfully as nitric acid, although much more slowly, and that the only sensation experienced during the production of even a deep eschar is a slight prickling.

All of the more powerful of the escharotics, when taken internally in sufficient amount, act as violent corrosive poisons, producing agonizing pain in the œsophagus and hypogastrium, violent bloody vomiting, often purging of similar character, and finally collapse, deepening into death, which is sometimes preceded by convulsions. When the dose is not so large, the patient may rally from the immediate effects of the poison, to succumb finally to the local lesions produced, or to struggle through a protracted convalescence to health, perhaps only to die years afterwards from organic stricture, caused by the ulcerations of the œsophagus or other of the digestive tubes. The first indication in poisoning by one of these substances is to neutralize or chemically antidote the poison : with the alkalies, dilute acid, generally convenient in the form of vinegar; with the acids, alkalies, usually at hand in the shape of whitewash or of soap ; with other poisons, specific antidotes. Opium should always be freely given, and the symptoms during and after the first poisoning be treated as they arise.

POTASSA. U. S.—*Caustic Potash* occurs in grayish, semi-translucent sticks, about three inches long and as thick as a large goose-quill, very deliquescent when exposed to the air, and extremely soluble in both water and alcohol. When it is placed upon the skin it soon melts, and, as it does so, gives rise to a pain which increases until it becomes very intense, and continues until the power of the alkali is so diminished that it can no longer reach through the tissue it has killed to the sound flesh below. Under the action of the escharotic the skin becomes of a dirty ashen-gray, and finally a slough is formed, with inflammation of the surrounding parts, and ulceration and detachment of the dead tissue in from six to ten days. The potash appears to act chiefly by abstracting the water, and, to some extent, by combining with the fatty and other portions of the tissues. Its slough being perfectly permeable, and its power being but slowly expended by its own action, potash is one of the most thorough of the escharotics : it is, therefore, to be preferred when a very deep and decided influence is required, as after the *bite* of a *rabid* dog. It is somewhat uncontrollable in its action, and requires care in its use. The best method of application is as follows. Take a piece of thick adhesive plaster, and cut a hole in it of such size that, when the piece is warmed and properly placed upon the skin, the part to be acted upon will be exposed while all around it will be protected. Then apply the plaster, and grease the outer surface of it, without allowing any of the oil to come in contact with the exposed central skin. Then lay the caustic potash upon the latter, and, when the action is believed to have extended deep enough, wash the part with dilute vinegar.

POTASSA CUM CALCE. U. S.— *Vienna Paste* is a grayish-white powder, composed of equal amounts of caustic potash and caustic—*i.e.*, unslaked —lime. It is not so active as caustic potash, but is less apt to spread and diffuse itself. It is to be mixed with sufficient alcohol to form a paste, and then applied like caustic potash.

Piedagnel[3] affirms that this caustic may be rendered nearly or entirely painless by mixing one part of morphine hydrochlorate with three parts of the powder, and then by the addition of chloroform forming a paste that may be spread upon lead plaster and so applied. In five minutes the skin under the application becomes of a dead-white color, and at the end of fifteen minutes is brown and carbonized. If the application be persisted in, the thickness of the eschar will become finally about equal to that of the layer of the paste employed. Cocaine would probably be more efficient in preventing pain than the morphine.

ACIDUM ARSENOSUM. U. S.—As a caustic, *arsenic* is energetic and powerful, but somewhat slow, and causes intense pain, with violent inflammation of the neighboring parts. It is stated to affect more rapidly morbid than normal structures, and is especially used for the destruction of malignant growths. It appears to act chiefly upon the vitality of the part, acting, when sufficiently diluted, as a powerful irritant, and when in a concentrated form producing an irritation so intense that life cannot endure it. Hence, probably, the reason of its affecting more rapidly morbid growths, which have a lower vitality than sound tissues.

The great objection to the employment of arsenic is the possibility of its absorption in sufficient amount to cause constitutional symptoms: even death has resulted from its external use. Since absorption takes place much more rapidly in a healthy than in an intensely inflamed or a dead tissue, whenever arsenic is employed as a caustic it should be used so freely as to kill the tissues rapidly, and under *no* circumstances should it be applied to a fresh wound. Used in any way, arsenic is a hazardous caustic, and it ought to be employed only with the knowledge and distinct remembrance of this fact. *Cancer*, and perhaps some forms of semi-malignant ulceration, such as *lupus*, appear to be the only diseases which justify its use.

There is no reason for believing that any of the almost innumerable substances which have been proposed as a basis for arsenous pastes possess peculiar advantages: the only needful direction is to mix the caustic with from eight to ten times its bulk of inert material of such a nature as to make either an ointment or a paste, and to allow this to remain on the part for from eighteen to twenty-four hours.

ZINCI CHLORIDUM. U. S.—*Zinc Chloride* occurs in broken fragments of a grayish-white color, translucent and waxy in appearance, of an acrid corrosive, or, when diluted, acrid astringent, metallic taste. It is extremely deliquescent, fusible, volatilizable at a high temperature, and very soluble in both water and alcohol. Zinc chloride is a very powerful

caustic, producing, when applied in a concentrated form, intense pain lasting from six to eight hours, and a whitish eschar, which usually separates in from six to twelve days. Its penetrating powers are a little less, and its action more readily controlled, than is that of potash; its absorption does not endanger life, as is the case with arsenous acid; and it leaves a slough which is free from odor.

Canquoin's Paste is made by mixing zinc chloride with flour and water. The strength varies according to the purpose, the weakest paste containing only one part of the caustic in six parts; the strongest, one part in three. When used, ten or fifteen drops of water are added to the paste, which is applied in layers, successive applications being required when a large tumor is to be destroyed. Anhydrous calcium sulphate has been especially commended by A. Ure, as forming a drier paste with the escharotic and limiting its action more definitely to the site of application than any other substance. Concentrated alcoholic or watery solutions of zinc chloride are often used as caustics in cases of *chancres* and other small *specific ulcers*, and are reputed to be efficient. They should be applied by means of little pledgets of lint. As the action of the chloride upon the skin is slow and very painful, whenever the cuticle over the part to be destroyed is sound it should be removed by means of blisters. By some surgeons the escharotic is introduced directly into the tumor to be destroyed. The official solution (LIQUOR ZINCI CHLORIDI, U. S.) has been used as a disinfectant, but is of very little value.

HYDRARGYRI CHLORIDUM CORROSIVUM. U. S.—*Corrosive Sublimate* is an escharotic of moderate power, which shares the dangers of arsenic, since death has followed its external use. In saturated solution it is much used as a caustic in *chancres*, but is scarcely equal to the solution of mercuric nitrate. In these cases it should be applied by means of a camel's-hair brush. The late George B. Wood recommended very highly that in *onychia maligna* a powder composed of equal parts of corrosive sublimate and zinc sulphate intimately mixed should be sprinkled thickly over the diseased surface, and a pledget of lint thoroughly wet with laudanum laid thereon. There is severe pain for half an hour to an hour; but the dressings are not to be removed until eight or ten hours have elapsed. When the slough which is thus formed separates, a healthy granulating surface is left.

LIQUOR HYDRARGYRI NITRATIS. U. S.—*Solution of Mercuric Nitrate* is a nearly colorless, highly corrosive, acid liquid, having a specific gravity of 2.100, and made by dissolving mercury, or its red oxide, in a large excess of nitric acid. Its application to a space not bigger than a half-crown has produced very serious poisoning.* It is rarely used, except for the purpose of destroying *specific* or *cancerous ulcers*.

* Case, *Lancet*, January 3, 1874.

It is especially useful in *chancres*, to which it should be applied with a glass rod. In obstinate *acne*, a minute drop applied by means of a glass brush to the top of an indolent tubercle is said to destroy it without producing a scar. It has been largely employed by gynæcologists in *ulcerations of the cervix uteri*. Its action is very prompt and is moderately deep; the pain is severe, but transient.

ACIDUM SULPHURICUM. U. S.—*Sulphuric Acid* is a powerful escharotic, and was formerly used extensively for destroying even large growths. For this purpose the strongest acid is mixed with charcoal, so as to make a thick, manageable paste. Before the application of this, the skin should be removed by a blister.

ACIDUM NITRICUM. U. S.—*Nitric Acid* is a powerful caustic, which is never employed to destroy large tumors, but is a favorite application to *chancres*, to *syphilitic*, *phagedenic*, and other unhealthy *ulcers*, and to *condylomata* and other small *dermal growths*. It is applied by means of a glass rod or a splinter of wood. A drop or two is usually amply sufficient; and when the action has gone far enough, the part should be washed with soapsuds, which at once neutralizes the acid.

ACIDUM CHROMICUM. U. S.—*Chromic Acid* occurs in anhydrous acicular crystals, of a deep red color, and an acid, metallic, corrosive taste. They are very deliquescent, melting down, when exposed to the air, into a deep red solution. Chromic acid is a very active oxidizer, and when mixed with organic matter rapidly alters it, and if in slight excess will dissolve almost any form of tissue. It is used to destroy *condylomata* and other *dermal growths*, and is best applied by means of a glass rod, the liquid formed by the spontaneous deliquescence of the crystals being used. Chromic acid is sometimes prescribed dissolved in, or made into a paste with, glycerin, but it is stated that in mixing the two great care must be taken to add the liquid slowly drop by drop, as otherwise there is danger of an explosion. In the German army, painting the sole of the foot and the skin between the toes with a five per cent. solution of chromic acid is said to have had a very great influence in increasing the marching powers of the troops, by arresting excessive sweating and hardening the skin. Chromic acid is a violent corrosive poison; a single drop of the saturated solution has produced very severe symptoms,* and in a number of cases death has resulted from its too free external use.†

BROMUM. U. S.—*Bromine* is a dark red liquid which has a very powerful, disagreeable, chlorine-like odor, and at ordinary temperatures emits

* Case, *Brit. Med. Journ.*, 1889, i.

† For experiments as to its effects on animals, see *Arch. f. Exper. Path. u. Pharm.*, vi.; also *Stricker's Jahrb.*, 1877, 139. For cases of poisoning, see *Ibid.*; *Schmidt's Jahrb.*, 1884, cci. 129; also *University Med. Magazine*, ii.

exceedingly acrid, pungent fumes. It is sparingly soluble in water, more soluble in alcohol, and still more so in ether. When brought into contact with organic matter, it oxidizes and completely destroys it with great rapidity. On account of this property and of its liquid form, bromine is one of the most severe, thorough, and rapid of all the caustics. It has not been much employed to destroy morbid growths, but has been found very efficient in *hospital gangrene*. After most of the slough has been cut away, the caustic should be applied pretty freely to the living tissue by means of a glass rod. When taken internally, bromine acts as a very powerful corrosive poison.*

Zinc Sulphate, *Copper Sulphate*, and *Burnt Alum* are feeble escharotics, never used except to destroy *exuberant granulations* in ulcers.

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* For cases, see *Schmidt's Jahrb.*, ccxxi.; also *Vierteljahr. f. Gerichtl. Med.*, 1889.

FAMILY XI.—DEMULCENTS.

THESE are bland substances, which form more or less gummy or mucilaginous solutions in water, capable of exerting a calming or soothing influence upon inflamed surfaces. Their action is probably purely mechanical, their adhesiveness causing the water they are in to remain long upon the part; they are, as it were, vehicles for water, the demulcent *par excellence*. It has been affirmed not only that demulcents soothe surfaces to which they are immediately applied, but also that taken internally they relieve irritation in distant organs. There is, however, no reason for supposing that such of them as escape digestion are absorbed or yield to absorption any principles in sufficient quantity to exert an influence upon the general system. The relief which undoubtedly follows their use in certain affections of parts which they can reach only through the circulation is probably due to the large quantities of water with which they are administered, lessening the concentration, and hence the acridity, of the urine and other secretions.

Clinically, demulcents are useful as local applications in all forms of acutely inflamed surfaces, and they are taken internally in acute *inflammatory* conditions of the *alimentary canal*. In slight *bronchial irritation* they are often of service, especially when allowed to dissolve slowly in the mouth: used in this manner, they not only exert an influence upon the mucous membrane of the mouth, but very probably find their way also into the respiratory passages.

ACACIA—GUM ARABIC. U.S.

A gummy exudation from Acacia Senegal, a small tree growing in Northern Africa, Senegambia, Guinea, etc., the Cape Colony, and Australia. Gum arabic occurs in roundish or irregular pieces, more or less transparent, hard, brittle, varying in color from white or yellowish white to red, or even deep orange brown. It consists of a peculiar, feebly acid, amorphous principle, *Arabin*, united with about three per cent. of lime, potash, and magnesia. In the plant, arabin, like other gums, appears to be formed by a retrograde metamorphosis of cellulose. On account of its solubility in water and pleasant taste, gum arabic is often used as a demulcent in *irritation* of the *fauces* and in *angina*. It is sometimes employed as an addition to drinking-water in fevers, and is believed to have slight nutritious properties. Its chief use, however, is in Pharmacy, in the making of emulsions, pills, etc. The mucilage (MUCILAGO ACACIÆ, U. S.) is used in various doses as a vehicle.

TRAGACANTHA. U. S.—*Tragacanth* is the concrete juice of Astragalus gummifer, and of other species of Astragalus, a small shrub of Asia Minor. Tragacanth occurs in large, whitish, horny, waved flakes, or sometimes in filamentous pieces. It is odorless and nearly tasteless. Introduced into water it does not dissolve, but swells up into a soft paste. One hundred parts of it contain, according to Guérin, 53.3 parts of arabin, 33.1 parts of bassorin, and 2.5 parts of inorganic ash. *Bassorin* is a gummy principle, at once distinguished from arabin by its not dissolving in water, but simply swelling up into a pasty mass. Tragacanth is used only in the manufacture of troches and in suspending heavy powders, for which purpose the difficulty of its solution and the extreme viscidity of its mucilage especially fit it. Its mucilage (MUCILAGO TRAGACANTHÆ, U. S.) is used in varying dose as a vehicle.

ULMUS. U. S.—*Slippery Elm* is the inner bark of Ulmus fulva, a large indigenous tree. The bark is of a yellowish-white or tan color, fibrous, yet when dry somewhat brittle, and occurs in long, flat strips or pieces one or two lines thick. It is pleasantly mucilaginous when chewed. It contains a large quantity of a peculiar mucilage, which it yields freely to water. Its infusion is sometimes taken in large quantities in *inflammations* of the *intestines*, as a demulcent laxative; but its chief use is as an external application. When ground into powder, slippery elm makes an excellent soothing poultice. The mucilage (MUCILAGO ULMI, U. S.) is used in varying dose as a vehicle.

CETRARIA. U. S.—*Iceland Moss* is the fronds of a lichen, Cetraria islandica, growing on rocks in Iceland and in most of the northern portions of the world. It is said to be abundant in the mountains of New England. The foliaceous, dry, shining, lobed, and laciniated fronds are about four inches long, of various intermixed colors, gray, brown, and red, and of a mucilaginous, bitter taste. Iceland moss contains a peculiar lichen starch and a bitter principle. It yields to cold water its bitterness; to boiling water all of its virtues. *Cetrarin* or *Cetraric Acid*, is the bitter principle, which may be obtained as a snow-white mass of interlaced acicular crystals. It unites with alkalies to form salts. With it in the lichen is associated in small quantities *lichenstearic acid*. Kobert has found that cetrarin has no effect upon the arterial pressure; also that in toxic dose it produces violent convulsions in the cat and in the dog, whilst in small dose it distinctly increases the activity of the motor area of the brain and spinal cord. Kobert[1] also asserts that in healthy men cetrarin increases the number of the red and, in a still greater degree, of the white corpuscles; and believes that in *chlorosis* and *anæmia*, especially when there is constipation, cetrarin will prove a valuable remedy.

Lichenin, or *Lichen Starch*, the mucilaginous, nutritive principle of Iceland moss, differs from ordinary starch in not being deposited in granules within the cells, but in layers or irregular masses between the cells, or indeed forming the walls

of the cells (De Bary[1]). In cold water it swells up without dissolving; in hot water it dissolves, and on cooling condenses into a jelly. With iodine it strikes a yellow, green, or sometimes rather faint blue, color. It is found in very many lichens; also in many species of sea-weed, notably in the so-called *Corsican moss*.

Iceland moss has enjoyed some reputation as a demulcent in pectoral complaints. From its bitter principle, it is probably somewhat tonic, and its lichenin is probably about equal to ordinary starch as a nutrient. When prepared as an article of diet, in the form of jelly, the bitter taste should be removed by soaking for some hours in a very weak, cold alkaline solution, and afterwards for a little while in cold water. Of the *Decoction* (DECOCTUM CETRARIÆ, U. S.), a pint may be given during the day.

CHONDRUS. U. S.—*Irish Moss*, or *Carrageen*.—The fronds of Chondrus crispus, and of Gigartina mamillosa, sea-weed growing on the coast of Ireland, and also on the northern coast of the United States, where it is now gathered in large quantities. The fronds are purplish red,—but, as kept in the shops, bleached by washing in fresh water, whitish and translucent,—cartilaginous, slender, much branched, swelling up but not dissolving in water, and having a slightly saline taste. Their virtue depends chiefly upon a starch- or gum-like principle, *Carrageenin*, which is distinguished from starch by not turning blue with iodine, and from gum by not precipitating from its watery solution on the addition of alcohol. Chondrus also contains a notable proportion of a vegetable albumin.

Carrageen, being demulcent and nutritious, is employed as an article of diet in those cases requiring food of such character, and may be used instead of arrow-root. It is to be prepared by first soaking for ten minutes in cold water, and then boiling from half an ounce to an ounce of it (according to the desired consistency) in a pint and a half of water down to a pint, sweetening and flavoring to taste. Milk may be substituted for water.

GLYCYRRHIZA. U. S.—*Liquorice Root* is the root of Glycyrrhiza glabra and glandulifera, native herbs of Southern Europe. It occurs in long, cylindrical pieces, from a few lines to more than an inch in diameter, brownish externally and yellowish within. Its fracture is fibrous, its taste sweet and mucilaginous, its odor none. Its active principle is *Glycyrrhizin*. This is a sweet, neutral substance, differing from the sugars in not being converted by nitric acid into oxalic acid, and by its inability to undergo the vinous fermentation. Liquorice root is very largely used as a demulcent in pectoral complaints, and, on account of its pleasant taste, as a means of disguising or of flavoring medicines. In the form of glycyrrhizin it is said to conceal almost entirely the bitter taste of quinine and similar substances. It is used almost exclusively in the form of the extract (EXTRACTUM GLYCYRRHIZÆ, U. S.), known as

Liquorice. The MISTURA GLYCYRRHIZÆ COMPOSITA, U. S., or *Brown Mixture*, contains paregoric, antimonial wine, and sweet spirit of nitre, and is much used as a domestic remedy in *colds* and the early stages of *mild bronchitis*. The dose for an adult is half a fluidounce to a fluidounce (15–30 C.c.) every three hours; for a child three years old, a teaspoonful (3.7 C.c.). The pure extract (EXTRACTUM GLYCYRRHIZÆ PURUM, U. S.) and the fluid extract (EXTRACTUM GLYCYRRHIZÆ FLUIDUM, U. S.) are excellent preparations. GLYCYRRHIZINUM AMMONIATUM, U. S., is an elegant demulcent preparation, which, however, is incompatible with acid or alkaline solutions: its dose is from five to ten grains (0.3–0.6 Gm.). The compound liquorice powder (PULVIS GLYCYRRHIZÆ COMPOSITUS, U. S.) contains senna and washed sulphur. It is an elegant laxative, acting, usually mildly and without the production of pain, in doses of one to two teaspoonfuls (4–8 Gm.).

LINUM, U. S., or *Flaxseed*, is the seed of Linum usitatissimum, or common flax, and contains large quantities of mucilage and of oil: its *compound infusion* is much used internally. It is often made with boiling water; but the application of too much heat causes the extraction of more or less of the oil, and thereby renders the preparation less palatable. The infusion should never, therefore, be boiled during its making. The addition of lemon and sugar renders it more palatable. It may be drunk *ad libitum* in pectoral *catarrhs*, in *enteritis* and *dysentery*, and in *irritation* of the *kidneys* or the *urinary passages*.

MEDULLA SASSAFRAS, or *Sassafras Pith*, yields a delicate mucilage much used in eye diseases (MUCILAGO SASSAFRAS MEDULLÆ, U. S.).

ALTHÆA. U. S.—The roots of Althæa officinalis yield a bland mucilage; their decoction is sometimes given in gastric irritation, and their syrup (SYRUPUS ALTHÆÆ, U. S.) is used as a vehicle.

HORDEUM.—The decorticated seeds of the common barley constitute the *pearl barley* of commerce. They contain starch and mucilage, and the decoction (DECOCTUM HORDEI) was formerly official. *Barley water* is used as a nutritious, demulcent drink in fevers and inflammatory conditions, especially when the gastric mucous membrane is involved. The U. S. Pharmacopœia of 1870 directed that it should be prepared as follows: "Take of barley two troyounces; water a sufficient quantity. Having washed away the extraneous matters which adhere to the barley, boil it with half a pint of water for a short time and throw away the resulting liquid. Then, having poured on it four pints of boiling water, boil down to two pints, and strain."

REFERENCES.

DEMULCENTS.

1. KOBERT . . . . . Verhand. d. Internat. Med. Cong., Berlin, 1890.

2. DE BARY . . . . Hofmeister's Handb. d. Physiol. Botan., ii. 255.

FAMILY XII.—EMOLLIENTS.

TRUE emollients are perfectly bland, fatty substances, which, when applied to the skin, soften it and render it more pliable. The action of these remedies is largely mechanical, and they probably soften the derm in precisely the same way as they affect a raw hide or a piece of leather. They are therefore especially useful when the skin has a tendency to crack or to chap. Whenever surfaces become sore by attrition, or, in other words, chafe, emollients are also useful mechanically. They often afford relief in simple inflammations of the skin under such circumstances that their action cannot be explained as purely mechanical: indeed, they seem to exert a dynamic influence upon the nutrition of the parts concerned. It may be that they shut out or interfere with the development of pathogenetic germs, or, in other words, that they are mechanical antiseptics. Be these things as they may, clinical experience has demonstrated that fatty matters are of very great value in the treatment of superficial inflammations. The blandest fat, when it becomes rancid, is very irritating, and will do more harm than good, so that the strictest attention must be paid to the condition of the fatty material employed. Any perfectly bland oily substance may be used as an emollient. *Mutton suet* and *goose-grease* are famous in domestic medicine, but are simply valuable because, if well prepared, they are less apt than are some other fats to become rancid. It cannot be allowed that there is any difference in fats, unless it be in penetrating power: a very hard fat is of course not so readily applied as a softer one, and therefore only such fats as freely melt, or at least become very soft, at the temperature of the body are to be used. *Common Lard* (ADEPS, U. S.), when freed by washing from the salt which it commonly contains, is a mild fat, melting at the temperature of the body. It is enormously used in pharmacy. *Cacao Butter* (OLEUM THEOBROMATIS, U. S.) is an absolutely bland vegetable fat, which is a firm solid at ordinary temperatures, but melts with the heat of the interior of the body, and is consequently very largely used in the preparation of suppositories, both official and magistral. *Spermaceti* (CETACEUM, U. S.) is employed to give consistence to ointments, as is also wax (CERA ALBA, or *White Wax*, and CERA FLAVA, or *Yellow Wax*, U. S.). *Cold Cream* (UNGUENTUM AQUÆ ROSÆ, U. S.), containing oil of sweet almonds, spermaceti, white wax, and rose water, is one of the most elegant of the official emollients.

OLEA.—Of bland fixed oils the U. S. Pharmacopœia recognizes four. Of these, the OLEUM AMYGDALÆ EXPRESSUM, U. S., or *Expressed Oil of Almond*, is a pale, straw-colored or colorless, almost inodorous oil, with a mild nutty taste. It may be employed wherever a very pleasant emollient oily application is desired.

OLEUM LINI, U. S., or *Linseed Oil*, is a yellowish oily liquid, with a peculiar odor and a bland taste. When exposed to the air it thickens and acquires a strong odor and taste. It is the least elegant of these oils, and is not often used in medicine, except when in *fecal accumulations* or other conditions large rectal injections of oil are required, when it is preferred on account of its cheapness.

OLEUM OLIVÆ, U. S., or *Olive Oil*, is expressed from the fruit of the European olive ; has a pale yellow or light greenish-yellow color, and a pleasant odor and taste. It is the ordinary salad oil of the table, and may be used wherever a very bland oil is desired. It has, however, no superiority for ordinary purposes over the OLEUM GOSSYPII SEMINIS, U. S., or *Cotton-seed Oil*, which is expressed from the seeds of the ordinary cotton-plant ; indeed, a very large proportion of the olive oil of commerce is cotton-seed oil : it is credibly affirmed that more cotton-seed oil is exported from New Orleans to the Mediterranean cities than olive oil is exported from those ports, most of the cotton-seed oil coming back with olive oil labels. There seems to be no sufficient reason for believing that olive oil differs from cotton-seed oil in its physiological or therapeutic properties. These oils are sometimes used internally with advantage, for nutritive purposes, and are also very mildly laxative. The assertion originally made by Kennedy, that large doses of olive oil are very useful against *biliary calculi*, has received strong clinical confirmation. S. Rosenberg[1] found that in dogs with biliary fistulæ olive oil not only increased the amount of bile, but also rendered the bile much more liquid. Since fats are absorbed chiefly, if not entirely, through the thoracic duct, it would appear that the oil must pass through the pulmonary circulation before reaching the liver. This is confirmed by the experiments of Chauffard, who could not find in the bile-duct or gall-bladder any trace of oil which he had injected into the stomach of the dog. If olive oil has the asserted remedial influence, it probably acts reflexly through the nervous system,—through a mechanism provided by nature for the purpose of aiding in the digestion of fats when in excess. The dose of the oil should be not less than from five to seven ounces (150–215 C.c.), taken in four to eight portions in not longer than three hours. It may be given in aromatized emulsion, with a little brandy or whiskey if desired.

LANOLIN is obtained from the wool of sheep, which is said to contain, on an average, forty-five per cent. of it. It appears to be practically the same as the natural oil of the hair in man and other animals.* It was

* See *Virchow's Archiv*, 1890, cxxi.

first recommended by Oscar Liebreich as a basis for ointments or preparations to be applied to the surface of the skin. It is entirely free from irritant properties, has the power of taking up a large amount of water without losing its unctuousness, does not easily become rancid, and it has been asserted that it is absorbed through the skin much more readily than are other fats. In the experiments of Patschkowsky,[2] half an hour after inunction with lanolin and potassium iodide the iodine was recovered from the urine, while official potassium iodide ointment yielded negative results. This has been confirmed by Kaspar,[3] but Ritter and Pfeiffer obtained contrary results, and in a considerable series of experiments were unable to perceive that lanolin had any superiority over other fats in promoting absorption. The facts, moreover, that lanolin is largely the secretion of sebaceous follicles, contains an abundance of cholesterin, and is of the nature of a waste product, which is intended, not for absorption, but for the keeping soft of the skin and its appendages, indicate very strongly that it will yield itself, and medicinal properties with which it may be impregnated, *less* readily to absorption than do other fats. As a basis of ointments used to medicate the skin it is most effective, but when absorption is desired it is inferior as a vehicle to ordinary fats.

GLYCERINUM—GLYCERIN. U.S.

This is a thick, syrupy liquid, colorless, free from odor, and of a sweet taste. Chemically speaking, it is *propenyl alcohol.* It is always set free during the process of saponification, and formerly was a by-product in the manufacture of soaps. At present it is made by the direct decomposition of fats by superheated steam.

Under certain circumstances, not well understood, glycerin forms hard, brilliant crystals. In its usual liquid form it mixes in all proportions with water and alcohol, and itself dissolves iodine, bromine, the alkalies, tannic and other vegetable acids, a large number of neutral salts, salicin, and other organic principles. It throws, however, most alkaloidal salts out of their watery solution.

Glycerin does not evaporate upon exposure, but is very hygroscopic, and absorbs water from the air. When pure, it is incapable of becoming rancid or of fermenting spontaneously. The acrid glycerin formerly so abundant, and still met with, owes its irritant properties to contaminating substances, especially, it is said, to oxalic and formic acids.

Physiological Action.—When large doses of glycerin (in the dog eight or more parts per thousand by weight) are injected subcutaneously, death is produced in a period varying, according to the dose, from one hour to several days. The symptoms are loss of muscular strength, lethargy, bloody urine, vomiting, dryness of the mucous membrane, with marked thirst, fall of temperature, gradual extinction of both respiration and circulation, and finally convulsions and coma (Dujardin-Beaumetz and Audijé[4]). The convulsions occur earlier and are more severe when large doses are employed, and are then said to be tetanic, and to be

accompanied by a decided rise of temperature. The fall of temperature is, even in the milder cases, present only late in the poisoning, and is sometimes, if not always, preceded by a rise. After death intense congestion, with more or less softening of the tissue, is found in the lungs, kidneys, and intestines. So far as we know, the largest amounts of glycerin taken by the stomach in man have produced no other symptoms than those of mild gastro-intestinal irritation ; but Schellenberg[5] has reported a long series of cases in which serious, and in one instance fatal, poisoning followed the injection of glycerin containing iodoform, for *coxitis* and other diseases. The conclusion of Schellenberg, that the manifestations were due to the glycerin, is confirmed by the fact that they were those seen in the lower animals poisoned by injections of glycerin,—namely, loss of muscular strength, elevation of temperature, rapid pulse, albuminous bloody urine with tube-casts, and in the fatal case the lesion of acute parenchymatous nephritis.

Catillon[6] asserts that glycerin administered in small continuous doses exerts a decided effect upon nutrition, but the general drift of the present evidence is to show that glycerin has no distinct effect upon tissue-changes.

In Catillon's experiments, eight grains given daily to guinea-pigs caused a very marked gain in weight, with a lessened excretion of urea. In man an ounce daily also produced a decided diminution in the elimination of urea, which was not increased by increasing the doses of glycerin. The appetite in many cases was, after a little time, much improved, and then the increased ingestion of food produced an increased elimination of urea. The fact that an increase of food was permitted in these experiments shows, however, that the conditions of experimentation were not rigid enough to allow much weight to be attached to the result ; and the relation of glycerin to the elimination of urea has been investigated by L. Lewin,[7] by N. Tschirwinsky,[8] and by I. Munk,[9] with somewhat contradictory results. Of these experiments the most extensive are those of Munk, who seems to have used all proper precautions, and who found that glycerin has no effect upon the elimination of urea or upon the general bodily nutrition. The results reached by Lewin correspond with those of Munk. Tschirwinsky omitted fatty materials from the food, and found that while at first the elimination of urea was diminished, it afterwards, under the use of very large doses of glycerin, was increased.

Glycerin is absorbed from the alimentary canal, and when freely administered is in part eliminated and in part burnt up in the system.

Both Ustimowitsch[10] and Plósz[11] found a substance in the urine which they believe to be a derivative product of glycerin, while Catillon proved that it is not eliminated by the skin or, even when it purges, by the intestines. Catillon and Lewin recovered from the urine only a small proportion of that ingested, Tschirwinsky only 8.7 per cent., while Ludwig Arnschink[12] found that not more than thirty per cent. escapes from the body. Since a large proportion of ingested glycerin is oxidized in the body, it would appear that it is capable of replacing to some extent true fatty carbohydrates for the production of heat or energy, and, therefore, has food value. According to the calculations of Arnschink, two hundred and nineteen parts of it are equivalent to about one hundred parts of fat. This view is corroborated by the work of Scheremetjewsky, who found in rabbits that the intravenous injection of glycerin was followed by an immediate increase of the consumption of oxygen, and of the giving up of carbonic acid.

The work of Scheremetjewsky has given rise to considerable controversy, but the latest experiments, those of I. Munk, seem to lead to the conclusion that glycerin is capable of taking the place of the bodily fat.*

According to Fuchsinger,[13] the bloody urine produced by poisonous doses of glycerin contains an abundance of the coloring-matter of the blood, but no free corpuscles. Very interesting in connection with the use of glycerin in diabetes is the assertion of Fuchsinger,[14] that in rabbits slightly poisoned with glycerin no sugar appears in the urine after the "diabetic puncture." The experiments of Eckhard [15] gave, however, a contrary result, and Catillon affirms that given in very large continuous doses glycerin increases the amount of sugar in the blood.

THERAPEUTICS.—Locally applied, glycerin is usually unirritating, and it is much employed as an emollient. The chief disadvantage that attends its use is its stickiness; on the other hand, its non-volatility and its hygroscopic properties give a persistency to its action which is often very advantageous. It enters largely into the composition of popular emollient ointments, or "creams," as they are called, and is often used itself for *chapped hands*, *excoriations*, and similar troubles. It is also employed by dermatologists to some extent in *chronic eczema;* in *seborrhœa*, whether affecting the hairy scalp or other parts, it is asserted to be especially useful, softening the masses of secretion, and, used in conjunction with such remedies as borax, zinc, and lead acetate, diminishing the amount of secretion. When there is a want of sebaceous secretion, it is said also to act efficiently; in *scabies*, *pruritus*, and even *psoriasis*, glycerin is used, diluted with water, as a vehicle for more active remedies. Upon the mucous membranes glycerin acts very much as it does upon the skin, and diluted with water is very useful in *coryza*, and even, by enemata, in *dysentery;* in *croup* or *laryngitis* it may with advantage be applied freely by means of a large camel's-hair brush to the orifice of the larynx, so as to run into the latter. In laxative doses it is asserted to be very effective in *hemorrhoids*. It also forms an excellent basis for mouth-washes; or a paste may be made with it and borax, or similar substance, for use in ulcerations of the same cavity. The list of diseases in which this remedy is employed might be very much lengthened; but the examples already given are sufficient to indicate the range of its application as an emollient and as a vehicle. There are certain persons upon whose skin and mucous membranes even the purest glycerin seems to act as an irritant. This influence is most intense when the glycerin is nearly or entirely free from water. It is, however, discernible even when the remedy is much diluted, and often inhibits its use. The existence of this idiosyncrasy to glycerin can be determined only by trial.

When administered internally in doses of one or two ounces, glycerin acts as a gentle but very uncertain laxative. It was proposed many years

* For discussion, see *Archiv f. d. Ges. Phys.*, 1889–90, xlvi.

ago as a substitute for cod-liver oil in *cachectic diseases*, but has failed to come into use. It has also been highly commended in *diabetes*,* but is of no service. It is valuable as a harmless substance which has the power of disguising nauseous medicines. In this way it may be employed with castor oil, in emulsions of turpentine, in solutions of iron, and in various mixtures. It seems, as it were, to envelop the medicinal substances and prevent their acting on the palate. *Plasma* or *Glycerite of Starch* (GLYCERITUM AMYLI, U. S.) is often used as a protective; *Glycerite of Yolk of Egg* (GLYCERITUM VITELLI, U. S.) is chiefly employed in making emulsions.

GLUSIDUM. Br.—GLUSIDE. SACCHARIN.†

Saccharin is a substance discovered by Fahlberg in 1879. Chemically it is an imide derived from the toluene of coal-tar. It occurs as a white powder composed of irregular crystals, very slightly soluble in water, readily soluble in glycerin, alcohol, and ether. Its watery solution has a distinctly acid reaction, and it forms salts. Its most remarkable property is its sweet taste, which is said to be three hundred times more intense than is that of sugar, so that if one grain of it be dissolved and neutralized in about ten pints of water its presence can still be recognized. Taken internally, saccharin is rapidly absorbed; it is eliminated unchanged chiefly through the kidneys, Bruylants[16] having recovered about eighty per cent. of it from the urine. It has been found by Bruylants in the milk of a nursing woman, and by Hedley abundantly in the saliva. Its influence upon man and animals is very slight; Mosso and Aducco administered seventy-five grains to a man without sensible effect, and found that frogs will live for months in a solution rendered neutral with soda; also, that six hundred grains given to a dog during ten days caused no change in the daily renal excretion of water, urea, hippuric acid, sulphuric acid, or phosphoric acid, and no alteration of the weight or of the general health. On the other hand, it appears to have a feeble influence upon various fermentations. Its solution has antiseptic properties, and in Plugge's numerous experiments it checked the action of ptyalin, pepsin, trypsin, and other allied ferments. Sawitzki, indeed, alleges that it depresses proteid metabolism.‡ In Bruylants's trials it failed to check artificial gastric digestion, probably on account of the acidity of the solution, but as little as one per cent. is enough distinctly to lessen the activity of pancreatin solutions. The general innocuousness of saccharin is, in accord with our own experience, asserted by Salkowski,[17] by Bruylants, by Dreschfeld,[18] by Levenstein,[19] and by other clinicians. Mixed with sodium bicarbonate, two parts to three, saccharin becomes

* For literature and discussion of point, see *Ziemssen's Encyclopædia*, xvi.

† The present is probably as good as any other place in this treatise to notice a substance whose use in practical medicine depends upon its lack of medicinal properties. On account of its being a proprietary or patented drug it is not recognized by the U. S. Pharmacopœia.

‡ See *Sajous's Annual*, 1891.

soluble. Its chief value in practical medicine is as a substitute for sugar in *diabetes*, *obesity*, and other diseases in which sugar is contra-indicated, but the observation of James Little,[20] that when freely given it is of great antiseptic value in the treatment of *ammoniacal urine*, from cystic, phosphatic, or other diseases producing retention or fermentation, is probably correct. It may be used freely as an article of diet, in the form of a solution in glycerin ; for medical purposes it is sometimes administered in compressed pills : dose, five grains (0.3 Gm.).

PETROLATUM.—Under the names of *vaseline*, *cosmoline*, etc., various yellowish fat-like substances are sold which are obtained by distilling off the more volatile portions of American petroleum. The basis of all these substances is paraffin, and their consistency varies in accordance with the proportion of the liquid hydrocarbons present. The U. S. Pharmacopœia recognizes PETROLATUM SPISSUM (U. S.), *Hard Petrolatum ;* PETROLATUM MOLLE (U. S.) (Br.), *Soft Petrolatum ;* and PETROLATUM LIQUIDUM (U. S.) (Br.), *Liquid Petrolatum.* All the cosmolines are insoluble in water, do not become rancid, are free from irritating properties, and act mechanically on the skin like fats. They are used as local emollient applications to the skin and mucous membranes and as a basis for ointments. When taken internally in the dose of a drachm to an ounce they exert no influence upon the system, but act locally upon the mucous membrane of the alimentary canal, allaying irritation and provoking soft fecal discharges.

POULTICES.—Poultices are moist, soft, scarcely adhesive, perfectly bland plasters, used to a very great extent to combat superficial inflammation. Poultices are much more powerful agents than are the true fatty emollients, and are correspondingly more capable of being abused : the results of such abuse will be spoken of directly. A poultice may, of course, be stimulating and irritant if made of such a substance as mustard ; but the ordinary emollient or true poultice is prepared out of some bland material which is totally free from action upon the skin, and depends for its remedial power solely upon the warmth and the water which it contains. Water, when pure and of a temperature approximating that of the body, is a sedative, checking all action, possibly by a direct influence, but probably by the merely mechanical acts of dilution of the pabulum and of separation of the germinal granules. It is also a relaxant, rendering all tissues soaked in it soft and yielding.

Poultices are sometimes applied in the early stages of phlegmonous and other superficial inflammations, for the purpose of checking the morbid action. Their influence is in such case simply one of sedation, and they are certainly not so efficient as the cold-water dressing. They are, however, especially useful in the advanced stages of inflammation, when suppuration has already commenced or is about to set in. Clinical experience has demonstrated that they then favor the formation of

pus. Further, the poultice in the latter stages of a superficial phlegmon not only hastens the formation of pus in the inflammatory focus, but lessens irritation in the outlying parts by its sedative action, and so softens the tissues as to aid in the passage outward and the discharge of the inflammatory products. When poulticing is too long persisted in, the part becomes pale or white, swollen, relaxed, and has a sodden look ; the granulations of the ulcer or abscess are large, pale, and very flabby, and all the vital actions are below the normal point. It is possible that even death of a part might be brought about by continuous poulticing. Be this as it may, after the discharge of pus, whenever the parts put on the aspect just spoken of, the poultice should be removed and stimulating applications substituted.

Any material which is in itself physiologically inert, and will long retain water, may be used as the basis of the poultice. *Flaxseed meal* is cheap, and is probably the most used of any substance. *Ground slippery elm* makes a very elegant mucilaginous poultice. Ordinary *Indian-meal mush* is often used. The *bread and milk poultice* is non-irritating, but is prone to undergo putrefaction. The poultice is rarely aseptic, and is often a carrier of germs. This in a measure may be prevented by boiling the poultice just before putting it on ; but even with this precaution, when applied to an infected wound, poultices, by retaining and stimulating the growth of germs, often increase the inflammation. For this reason other methods of applying warmth and water have largely replaced the old-fashioned poultice. Spongiopiline, or absorbent cotton, or similar material, which is readily rendered aseptic, and is incapable of undergoing fermentation, when saturated with heat and water affords an application which is practically a poultice, and which may be rendered germicidal by the addition of minute quantities of corrosive sublimate or similar substances, as called for by the exigencies of the case.

Poultices are frequently used in the treatment of deep-seated inflammations. Under these circumstances, according to the dictates of experience, they should be applied very hot, and be frequently renewed ; very often, too, a small amount of mustard or of some similar stimulating material is added to them with advantage. As a result, these poultices act as gentle but deep-reaching counter-irritants, which in all likelihood affect not merely the blood-vessels of the skin, but also those of the subdermal tissue. When it is borne in mind that in all these cases the poultice is applied to a very large surface, it will readily be perceived that this counter-irritation is a powerful one. Thus, in *pleurisy* or in *pneumonia* the whole anterior or posterior surface of the chest is covered, or perhaps the whole chest is enveloped, by the jacket-poultice. In *peritonitis* the poultice should be as large as the abdomen of the patient. In either of these cases the amount of blood drawn to the surface must be considerable. It is probable that the water of the poultice in some cases actually soaks through and exerts its direct sedative influence upon the affected tissue. The value of poultices in

lung diseases is much greater in children, whose chest-walls are very thin, than in adults; and it is not illogical to believe that the difference may be dependent upon the inequality of the chest-walls.

The *jacket-poultice* should be made of thin flannel formed into a sort of double bag, so cut and shaped as to fit the individual, and secured in front with safety-pins and over the shoulders with tapes, or it may be fastened directly to an undershirt, a piece of oiled silk always being placed directly outside of the jacket. The jacket should be divided into two parts by a horizontal line of stitching, and be filled from one end. In order to prevent sagging of the contents, it is well, after filling, to take a stitch here and there, in the manner of quilting. The effect of a jacket-poultice may be imperfectly attained by covering the patient with wool batting and oiled silk outside of this,—in fever patients the moisture from the surface and the heat of the body serving to form a kind of fomentation.

The value of the jacket-poultice in disease is, however, greatly lessened by the fact that it enormously increases the heat-retention of the body, and has, therefore, in many cases a very serious influence in heightening a fever temperature whose reduction is urgently indicated. Whenever, in a *pneumonia*, the temperature is high, the application of cold water by means of compresses, or absorbent cotton, is preferable to the use of the jacket-poultice. In cases of *peritonitis* the sensations of the patient are often a practical guide to the choice of the dressing. If the pain is aggravated by external warmth, the cold-water dressing is preferable; whilst, if the cold-water dressing is steadily obnoxious to the patient, the best results may usually be achieved by the use of hot water.

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FAMILY XIII.—PROTECTIVES.

In the present class are included those materials used by the physician as protective applications to the skin.

Adhesive plaster (Emplastrum Resinæ, U. S.) is used for mechanical purposes. It, however, irritates the skin somewhat, and consequently is rarely employed where protection is the only object. Under the latter circumstances, the lead plaster (Emplastrum Plumbi, U. S.) or the soap plaster (Emplastrum Saponis, U. S.) is preferable. These substances are free from irritant properties, but are only slightly adhesive, and are scarcely used except to protect the skin from pressure or friction, as when *bed-sores* are threatened. They should be spread upon very soft kid. It is important that they be not so thick or hard as to lose their pliability. If they are stiff, by their movements during the motions of the body they may do much harm. *Isinglass Plaster* (Emplastrum Ichthyocollæ, U. S.) is readily applied when simply dampened, and is much used domestically under the name of *court plaster.* Collodion (Collodium, U. S.) is a solution of pyroxylin in alcohol and ether, pyroxylin (Pyroxylinum, U. S.) being soluble gun-cotton, chiefly made up of the tri- and tetra-nitro-cellulose ; upon evaporation it leaves on the skin an adherent protecting film.

Physiologically, gun-cotton is inert. Collodion is a colorless, slightly opalescent liquid, of a syrupy consistence, and smelling strongly of ether. By long standing it deposits a layer of fibrous matter, and becomes more transparent. This layer should be reincorporated, by agitation, before the collodion is used. When it is applied to the skin, and the menstrua are allowed to evaporate, collodion forms an impervious, colorless, transparent, flexible, and strongly contractile film, which adheres very closely, and cannot readily be removed. The contractility of the film may in a great measure be destroyed by the addition to the collodion of certain substances, as in flexible collodion (Collodium Flexile, U. S.), which contains five per cent. of Canada turpentine and three per cent. of castor oil, and on evaporation leaves a film which does not contract. A collodion may be rendered actively medical by the addition of some principle soluble in its menstruum, as in cantharidal collodion.

As a substitute for collodion the non-official solution of gutta-percha in chloroform (Liquor Gutta-Perchæ) is sometimes employed.

DIVISION II.—EXTRANEOUS REMEDIES.

THESE are drugs which are employed not to act directly upon the human system or upon any of its tissues, but upon some extraneous material or entity either in the cavities of the body or upon its exterior. Thus, an antacid neutralizes acid in the stomach, or an anthelmintic kills the tapeworm in the intestines, or a disinfectant destroys poisonous emanations in the exterior world and thereby wards off disease.

FAMILY I.—ANTACIDS.

ANTACIDS are, strictly speaking, substances which are capable of neutralizing acid. The class, as here defined, contains those remedies which in medicine are used for the purpose of neutralizing an excess of acidity in the primæ viæ. They are almost solely employed in forms of *dyspepsia*. Without doubt, *cardialgia*, *gastric uneasiness*, *heartburn*, and the rising of sour water in the mouth are often the result of too much acid in the stomach, perhaps secreted by a perverted glandular action, but more probably in the great majority of cases formed by fermentative changes in the partially digested food. As excessive acidity of the stomach causes gastric uneasiness and derangement, so will a similar condition of the intestinal canal cause pain and spasm and functional disturbance in the bowels. This is seen most frequently in infants, and is very often associated with a diarrhœa in which the passages have a green color, similar to that of spinach, and hence are sometimes spoken of as "spinach-stools." In *diarrhœa* of this character, as well as in *colic*, antacids are often of service by neutralizing the acid in the intestinal canal.

Clinical experience has demonstrated that dyspepsia is often permanently relieved by the use of alkalies when they are given steadily day after day, about twenty minutes after eating, for a long time. According to Thomas K. Chambers,[1] this is dependent upon an effect pointed out by Claude Bernard,—the augmentation of the acid gastric juice, and so of the normal peptic powers of the stomach. The same authority further says, "The test of benefit being derived from an alkali is the dose not requiring to be increased as the patient goes on taking it, but,

on the contrary, being diminished gradually, while relief from the recurrence of heartburn continues still to be experienced."

Sick headache is sometimes dependent upon gastric irritation produced by an excess of acid in the stomach. This true sick headache is generally to be distinguished from migraine by the early occurrence of the stomach symptoms, either as heartburn, nausea, vomiting, or simple gastric distress, and by the fact that the pain comes on with an attack of blindness or of dizziness, and is not limited to any one spot, as the supra-orbital or other neuralgic foci, but is felt all across the brows. In this form of cephalalgia antacids often afford prompt relief.

Various substances which have already been discussed in this work are excellent antacids, most of them uniting this to other medicinal properties. Thus, when a stimulating antacid is desired, as is very often the case in sick headache, half a drachm of the *aromatic spirit of hartshorn* may be taken, well diluted with water. Again, when a laxative antacid is needed, a teaspoonful to a tablespoonful of *magnesia* may be exhibited. *Potassa* and its carbonates have already been dwelt upon with sufficient detail. They may be used as antacids; but, as they exert other powerful influences upon the system, they are, we think, not so generally useful as the soda preparations.

SODIUM.

Pure soda is an escharotic, and most of its salts are irritant. It is absorbed and eliminated freely.*

Soda being the only alkali of the blood, even very large doses of it have very little influence upon man or mammalia, but it is probable that it acts much more powerfully on cold-blooded animals.

Grandeau[3] found that one hundred and seven grains of sodium carbonate injected into the vein of a dog produced only very slight symptoms, and that thirty-five grains of the nitrate similarly administered to a rabbit caused only some convulsive movements. According to Guttmann,[4] however, the sodium salts thrown directly into the blood in very large amounts will slowly cause death, the agony being very prolonged, and, when the chloride is used, convulsions being developed. Both Podocaepow and Guttmann assert that even the largest doses do not sensibly affect the heart or the temperature; and the latter observer further declares that they are without influence upon the nerve-centres, the peripheral nerves, or the muscles. But if this be the case, it is difficult to perceive how they can cause death; and the earlier experiments of Podocaepow indicate that they do exert a very feeble action upon the peripheral nerves or the muscles. Curci[5] also finds that the sodium salts increase the blood-pressure after the destruction of the oblongata, and believes that they influence the peripheral vaso-motor nerves. H. G. Beyer,[6] as the result of experiments made upon terrapins, comes to the conclusion that sodium salts excite first the ganglia of the vaso-dilator nerves and afterwards those of the vaso-motor nerves.

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* As Rabuteau[2] found that in dogs with gastric fistula both the quantity and the acidity of the gastric juice are decidedly increased by the use of salt meat, it would appear probable that the local action of common salt upon the stomach is that of a stimulant.

Although Mayet[7] affirms that sodium chloride increases the elasticity of the red blood-corpuscles, the immediate influence of the sodium salts upon the blood * is probably very slight, since, according to Podocaepow,[8] one part dissolved in twelve parts of blood does not affect either the physical characters of the red corpuscles or the intensity of the ozone reaction.

Podocaepow and Schönlein[9] both affirm that they cause in the frog spinal convulsions, but in Ringer and H. Sainsbury's[10] experiments the influence of the sodium salts upon the frog was found to be so slight that they could hardly be made to kill. It seems established, however, that they will produce cataracts in the frog.† Most observers state that the sodium salts are capable of arresting the frog's heart in diastole, either when it is in position or after it is removed from the body; and Laffout[11] states that there is a primary period of cardiac stimulation, which is in accordance with the observation of T. W. Mills[12] upon fishes. There is, however, much difference of statement by different observers in regard to the action of these salts upon the frog's heart.‡

Nutrition.—A certain amount of soda is a necessary food for the higher animals, yet it is very doubtful whether an habitual excess has decided effect upon the nutrition, the general drift of the present evidence being to show that when in excess the sodium salts neither increase nor yet decrease the elimination of urea or other products of tissue-waste.

In the experiments of Münch[13] the continuous exhibition of large doses of common salt to man apparently produced at first a slight diminution of excretion and a corresponding gain of the body in weight; but after a time the excretion increased and the weight of the body decreased. The variations in excretion affected chiefly the urine, but sometimes the perspiration and fæces were also influenced. The urine was rendered alkaline, but its solid ingredients were scarcely at all affected. The conclusion of Damourette and Hyades,[14] that salt increases the elimination of urea and uric acid, is not warranted by their own experiments; and in the researches of I. Mayer,[15] of A. Ott,[16] of C. Clar,[17] and of L. Klemptner,[18] neither the sodium citrate, acetate, phosphate, nor sulphate increased nitrogenous elimination.

THERAPEUTICS.—The fact that soda, in moderate amount, has no depressing action, and indeed very little, if any, influence upon the general system, renders it preferable to potash in cases of acidity of the primæ

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* Kowalewsky records in the *Centralbl. f. Med. Wissen.*, 1887, the results of an elaborate study of the effects of adding, either in solid form or in concentrated solution, salts of potassium, sodium, lithium, and ammonium to the blood. As it is not possible at present to connect this influence with the effects of therapeutic doses of the drug inside of the body, we content ourselves with referring to the paper.

† For a discussion of this, and literature on the subject, see Limbourg (*Arch. f. Exper. Path. u. Pharm.*, 1888, xxiv.). For a series of papers on the antagonistic actions of sodium, potassium, and calcium salts on the frog, by Sydney Ringer, see *Journal of Physiology*, 1890, 1894, 1895.

‡ See Podocaepow (*Virchow's Archiv*, xxxiii. 507), Schönlein (*Arch. f. d. Ges. Physiol.*, xviii. 26), Laffout (*Compt.-Rend. Soc. Biol.*, 1880, 282), Ringer and Sainsbury (*Lancet*, 1882, ii. 736), Ringer (*Brit. Med. Journ.*, 1884), Limbourg (*Arch. f. Exper. Path. u. Pharm.*, 1888, xxiv.).

viæ. It is *par excellence* the alkali for *acid dyspepsia*. On the other hand, the circumstance clearly established by Roberts,[19] that it is less powerful as a solvent of uric acid than is its sister alkali, together with the property, believed to belong in a much greater degree to potash, of preventing the formation of uric acid, makes soda of very inferior value in *uric acid gravel* or *uric acid diathesis*. When in any case it is desirable simply to render the urine alkaline, and at the same time to avoid depressing the system generally, soda would, on theoretical grounds at least, seem preferable.

It appears to be well proved, clinically, that the alkaline sodium salts given one to two hours before meals in full doses are of decided value in the treatment of *chronic hepatic torpor*, of *catarrhal jaundice*, and especially of *gall-stones* or other affections associated with excessive viscidity of the biliary secretions.

As the result, however, of an elaborate series of experiments made upon dogs with biliary fistula, J. Glass[20] concludes that the alkalies given by the mouth do not increase the alkalescence or amount of the bile. The caution necessary in applying such experiments to human medicine has been spoken of in an earlier chapter. Moreover, it was apparently proved by the experiments of S. W. Lewaschen that the sodium carbonate, sulphate, or phosphate, given to dogs with biliary fistula, increases very markedly the liquidity of the bile by diminishing the percentage of solids. The sodium salicylate acted similarly to, but much more powerfully than, the other salts. E. Dufourt, experimenting with the sodium bicarbonate upon dogs, found that there was a very constant and pronounced increase both of the glycogen and of the sugar of the liver.

Although so harmless, the sodium salts when in great excess are decidedly irritant, and it has been shown by Stokvis[21] and Levi[22] that it is possible with the sodium chloride to produce albuminuria, tube-casts, and organic renal changes.

The following are the antacid preparations of soda; the pure bicarbonate should usually be selected, as being the least irritant.

Soda. U. S.—*Caustic Soda* occurs in grayish-white fragments, which deliquesce on exposure and subsequently absorb carbonic acid. It is an active escharotic. The solution of soda (Liquor Sodæ, U. S.) contains about five per cent. of sodium hydrate, has a specific gravity of 1.059, and is too acrid for practical use.

Sodii Carbonas. U. S.—*Sodium Carbonate* occurs in strongly alkaline, colorless crystals, which rapidly effloresce on exposure to the air, and fall into a white powder. It is very soluble in water; by heat its water of crystallization is driven off, and the official *Dried Carbonate* (Sodii Carbonas Exsiccatus, U. S.) is left. *Commercial Sodium Bicarbonate* (Sodii Bicarbonas Venalis) is a white, opaque powder, containing variable amounts of soda not fully saturated with carbonic acid. Pure *Sodium Bicarbonate* (Sodii Bicarbonas, U. S.) should

always be selected for internal use. The antacid dose of these preparations is ten to twenty grains (0.6–1.2 Gm.).

Sodium Nitrate (SODII NITRAS, U. S.) and *Sodium Acetate* (SODII ACETAS, U. S.) are never used in medicine.

CALX—CALCIUM.

When calcium carbonate (marble, limestone) has its carbonic acid driven off by heat, certain white or grayish-white masses are left, constituting the unslaked lime of commerce (CALX—*Lime*, U. S.). When to this lime is added about half its weight of water, there is formed a white powder, calcium hydrate, or slaked lime.

Unslaked lime is an active escharotic; slaked lime is an irritant, or, when in concentrated form, a feeble escharotic.

Lime is never used in substance in medicine, but in the form of a watery solution. When in such dilute form it acts as a detergent and sedative, especially to mucous membranes. Its official insoluble preparations are free from irritant properties and are mild astringents. Neither the soluble nor insoluble preparations of lime are absorbed to any large extent, the lime escaping, if given in considerable dose, in great part with the fæces in the form of some insoluble salt. Minute quantities of it probably circulate in the blood in combination with proteids.

When a soluble salt of calcium is given intravenously, an insoluble form of lime is probably rapidly deposited in the tissue. Excretion of lime chiefly takes place through the urine, or perhaps more largely through the large intestine.

PHYSIOLOGICAL ACTION.—Probably owing to the difficulty of their absorption, even the soluble preparations of lime have not been found in practical medicine to have any general effect upon the body. Carl Franke, indeed, states that the intravenous injection of large amounts of soluble lime salts has no effect upon rabbits.

It is certain that the lime salts are required for the processes of nutrition, but it would appear that a sufficiency of these lime salts is under ordinary circumstances supplied to the system by the food, so that no gain is to be achieved by the further administration of lime.

The soluble salts of lime are evidently not without physiological activity, and have close relation with the general bodily well-being. W. H. Howell and E. Cooke[23] have proved that the inorganic salts of the blood, milk, gastric juice, etc., are able to keep the isolated frog's heart beating with force and regularity for many hours without other food, and, according to the experiments of Ringer, among these salts those of lime are especially important. Further, it seems to be demonstrated that small doses of soluble calcium salts increase the energy of the heart's action, as the experiments of Ringer[24] have been confirmed by Mickwitz and also by Binet. Binet[25] states, however, that though the cardiac arrest usually takes place in systole in calcium salt poisoning, yet if the salt have come directly in contact with the heart in concentrated form there is paralytic arrest (diastolic). Further, according to Ringer[26] and to H. G. Beyer,[27] the voluntary and involuntary

muscles of the frog are stimulated by small amounts of lime; and, according to Franke,[28] they are paralyzed by large amounts of the drug. Stefani[29] states that calcium chloride when applied locally in minute amount increases the functional activity of the motor nerve-trunks, but when in large amount produces rapid paralysis; whilst Binet has demonstrated that the toxic dose of the calcium salt directly paralyzes the cerebral cortex and the motor centres of the spinal cord.

LIQUOR CALCIS. U. S.—*Solution of Lime.—Lime-water* is a colorless liquid, having the sp. gr. 1.0015, and containing about 0.15 per cent. of lime. It has an alkaline taste, and is nearly destitute of irritant properties. On exposure to the air it absorbs carbonic acid and deposits calcium carbonate. Twenty minims of syrup of lime (SYRUPUS CALCIS, U. S.) equal a fluidounce of lime-water.

THERAPEUTICS.—Lime-water is used exclusively as a local remedy. In *vomiting*, from almost any cause except acute gastritis, equal parts of lime-water and milk afford an elegant, simple, and much-used remedy. If the vomiting be severe, all other food should be inhibited, and one or two tablespoonfuls of the mixture given every half-hour,—the quantity, as well as the proportion of milk, being increased as the stomach is able to bear it. As lime-water when put in milk prevents the formation of dense coagula, it is often added with advantage to that fluid when used as food for infants, or for adults with weak digestion. As an alkaline astringent, the *syrup* is often useful in *diarrhœa* in doses of one to two fluidrachms (4–7 C.c.), well diluted.

Externally, lime-water has been used as a wash in various skin diseases, especially in *tinea capitis:* it is also applied to *ulcers*, and is said to have a very marked influence in lessening the amount of discharge. When mixed with an equal bulk of linseed or olive oil (LINIMENTUM CALCIS, U. S.), lime-water forms a thick, soapy liquid (*Carron Oil*, so called from the name of the iron-works at which its reputation was first made), which is much used in recent *burns*.

Lime-water has the power of dissolving mucus and also false membrane, and has therefore been introduced as a local remedy in *pseudo-membranous croup* and in *diphtheria*. It is sometimes used by causing the patient to inhale the vapors of slaking lime, but a better method is to pulverize lime-water by means of an atomizer and direct the spray upon the back of the fauces while the patient is respiring deeply. The application should be made every two or three hours.

CALCIUM CARBONATE.

Chalk is the native, friable calcium carbonate, a milk-white, soft solid, of an insipid, earthy taste, insoluble in water, wholly soluble, with effervescence, in dilute muriatic acid. CRETA PRÆPARATA. U. S.—*Prepared Chalk* is chalk freed from impurities by pulverization, levigation, and elutriation; a white, perfectly smooth powder. CALCII CARBONAS PRÆCIPITATUS. U. S.—*Precipitated Calcium Carbonate* is a white powder, free from grittiness, which is made by precipitating calcium

chloride with sodium carbonate. Dose of either preparation, twenty grains to a drachm (1.3–4 Gm.).

THERAPEUTICS.—Calcium carbonate in its different forms is used internally as an antacid and a very mild astringent. As none of the salts which it forms are purgative, it, with the other preparations of lime, is the best antacid when *diarrhœa* is present. The crude chalk should never be used, but the other preparations are probably of equal value.

Some practitioners assert, however, that the oyster-shell is more acceptable to delicate stomachs, on account of the animal matter which it contains; and, under the name of *Castillon's Powder*, a mixture of salep, tragacanth, sago, of each three parts, prepared oyster-shell one part, and cochineal sufficient to color it, has been much used in obstinate *summer diarrhœas*. A drachm of this is boiled in a pint of milk, and the decoction taken as food *ad libitum*.

Chalk Mixture (MISTURA CRETÆ, U. S.) contains thirty grains of chalk to the ounce; dose, one to two tablespoonfuls (15–30 Gm.). It is often combined with laudanum or paregoric and tincture of kino or catechu.

Externally, prepared chalk and precipitated calcium carbonate are used as desiccants and protective applications to *ulcers* and *chronic burns*, also in *excessive sweating* of the feet, and in *intertrigo* and other *affections of the skin*.

CALCIUM HALOID SALTS.—Germain Sée[30] has called attention to the value in practical therapeutics of the calcium bromide and iodide, asserting especially that they improve digestion, and that they are absorbed and eliminated with rapidity. *Calcium Bromide* contains eighty per cent. of bromine (against the seventy-seven and a half per cent. of the sodium bromide, the sixty-seven per cent. of the potassium bromide, and the sixty-five per cent. of the strontium bromide), and ought to be useful in *epilepsy*. The calcium bromide is a very deliquescent soluble salt, which must be given in solution. The dose is probably that of the alkaline bromides. *Calcium Iodide* contains eighty-six per cent. of iodine (against the eighty-three per cent. of the sodium iodide, the seventy-six per cent. of the potassium iodide, and the seventy-four per cent. of the strontium iodide). *Calcium Chloride* (CALCII CHLORIDUM, U. S.) is locally a violent irritant, but it is strongly recommended by Sée in the treatment of *gastric catarrh* and fermentative *dyspepsia*. Dose, fifteen to seventy-five grains a day (1–5 Gm.).

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FAMILY II.—ANTHELMINTICS.

THESE are medicines which kill or cause the expulsion of intestinal worms. They are sometimes divided into *vermicides*, those which kill, and *vermifuges*, those which expel ; but there is little or no practical use in the division. It is of much greater importance to establish the relations between these drugs and the different species of entozoa, since clinical experience has demonstrated that an anthelmintic very efficient against one form of intestinal worm may be not injurious to another species. Therapeutically considered, the entozoa may be divided into the *Tapeworms* (*Tæniæ*), the *Round-worms* (*Lumbrici*), and the *Seat-worms* (*Ascarides*). The last of these differ from the others in that they are to be attacked solely by enemata.

It is obvious that the value of an anthelmintic depends not only upon its power of poisoning the articulate, but also upon its harmlessness as regards the patient. Thus, it is the eminent combination of these qualities that renders the infusion of quassia so valuable in cases of seat-worms, while carbolic acid, though very efficient, should never be used against the same parasite, since it has greatly imperilled, if it has not destroyed, the life of the patient when so employed.

There are certain general rules which govern the administration of anthelmintics, and which should not be lost sight of. They may be summed up as follows :

Let the alimentary canal be as empty as possible, so that the drug may act with the greatest force upon the enemy. For this reason, anthelmintics are best administered early in the morning ; and in obstinate cases the patient should be required to fast until dinner-time. If the drug be not itself a purgative, from four to eight hours after its administration a brisk cathartic should be given ; or a purgative dose of calomel may be combined with it, as the bilious purging induced by the latter drug seems to be especially obnoxious to the entozoa.

SPIGELIA—PINKROOT. U.S.

The root of Spigelia Marilandica, an herbaceous perennial, growing in the Southern and Southwestern United States. It consists of a knotty head, with numerous fine, crooked, branching rootlets. The odor is faint and peculiar ; the taste sweetish and slightly bitter. W. L. Dudley

separated from it an alkaloid, *spigeline*, which, according to Boorsma,[1] is actively poisonous.

PHYSIOLOGICAL ACTION.—Full therapeutic doses of spigelia produce in man no symptoms, but, according to Hodge Thompson (quoted by Eberle), Eberle,[2] and Spalsberg,[3] an overdose causes acceleration of the pulse, dilatation of the pupils, heat and dryness of the skin, flushing and a swollen appearance of the face, with, in Eberle's cases, talkative delirium. Two fatal cases* of poisoning by it are said to have been recorded. According to H. A. Hare,[4] toxic doses slow the pulse and depress the heart, the respiratory centre, and the motor spinal cord.

In Hare's experiments toxic doses of spigelia caused in the dog hurried respiratory movements, retching, wide dilatation of the pupil, internal strabismus, marked exophthalmia, muscular weakness and loss of coördination, and at last sleep, passing into coma and death from failure of respiration; in the frog exophthalmia, excessive muscular weakness, loss of reflex activity, and slowing of the heart, with at first increase of power of the systolic contractions but afterwards arrest in a condition of semi-diastole.

THERAPEUTICS.—Spigelia is a most efficient remedy in cases of the round-worm, and is, when given within the bounds of moderation, entirely safe. It appears to narcotize the worm, and requires the use of a brisk cathartic. The fluid extract (EXTRACTUM SPIGELIÆ FLUIDUM, U. S.) is efficient in doses of two fluidrachms (7 C.c.). A better preparation is the *Fluid Extract of Spigelia and Senna* (EXTRACTUM SPIGELIÆ ET SENNÆ FLUIDUM, U. S. 1870), which is much liked by children on account of its agreeable taste. The dose for an adult is one-half a fluid-ounce (15 C.c.); for a child two years old, one-half to one fluidrachm (2–4 C.c.), repeated every four hours until it purges.

AZEDARACH, the bark of the root of Melia Azedarach, or Pride of China, is used in the South as a remedy for the *round-worm*. It is said to possess poisonous properties similar to those of spigelia, yet it is affirmed that animals and children eat its fruit with impunity. It is usually given in decoction (two ounces to one and a half pints, boiled to a pint), the dose being for a child a tablespoonful (15 C.c) every two or three hours until the bowels are affected.

CHENOPODIUM, U. S., or *Wormseed*, is the fruit of Chenopodium anthelminticum, or Jerusalem Oak, a rank, odorous plant, growing about waste places in the suburbs of towns in the United States. It consists of minute, globular, light brown seeds about the size of a pin's head, of a nauseous odor and a pungent taste, due to the volatile oil which

* These cases appear to have been indefinitely copied, and are of doubtful authenticity.

they contain in large quantity. *Wormseed Oil* (OLEUM CHENOPODII, U. S.) is of a light yellow color, becoming darker and less fluid by age, of a peculiar powerful odor and a hot burning taste.* It has been used in *hysteria*, but is now employed only as an anthelmintic against the *lumbricus*, and more rarely the *tapeworm*. It is very efficient, and ten drops (0.6 C.c.) of it on sugar may be given to a child three years old, before breakfast, dinner, and supper, for two days, followed by a brisk purge.

CUSSO, U. S., *Kousso, Brayera*, is the female inflorescence of Hagenia abyssinica, a tree of Abyssinia. It occurs in compressed greenish-yellow clusters, of a fragrant balsamic odor, and a taste which in a little while becomes acrid and disagreeable.

The crystalline resin *Kosin*, discovered by Pavesi, is believed by Bedall[5] to be the active principle of kousso. Leichsenring affirms it to be *Kosotoxin*, an amorphous, yellowish-white substance, which, according to Handmann, is an active paralyzant to all muscles, including the heart, and also of the motor nerve-endings.

Brayera is a most efficient remedy against the *tapeworm*, and even in large doses causes no greater inconvenience to the patient than some nausea, abdominal pain, and looseness of the bowels. It is generally not necessary to administer any purgative with it, and the worm is discharged dead with the last watery passages. A half-ounce of the powdered flowers is given suspended in water in the morning, with the usual precautions as to diet. The best preparation is the yellowish-brown, impure, amorphous *kosin* of commerce, which may be given in doses of seven to fifteen grains (0.5–1 Gm.) repeated every half-hour until four doses have been taken, a full dose of castor oil being administered one hour later. Dose of the fluid extract (EXTRACTUM CUSSO FLUIDUM, U. S.), half a fluidounce (15 C.c.). Care should be exercised in giving brayera to pregnant women, as it is stated that it has produced abortion.

SANTONICA—SANTONICA. U.S.

Levant Wormseed consists of the unexpanded flowers and peduncles of Artemisia pauciflora, a composite of Northern Middle Europe and Asia. It consists of pale, greenish-brown, smooth heads of four or five tubular flowers of a very strong aromatic odor when rubbed, and a bitter, disagreeable taste. It contains volatile oil, resinous matter, and a crystalline principle, *Santonin* (SANTONINUM, U. S.), or *Santoninic Acid*, which occurs in colorless, pearly, four-sided, orthorhombic, very insoluble

* In the *Maryland Med. Journ.*, iv. 20, T. R. Brown reports a case in which death was attributed to the taking of an ounce or more of wormseed oil in divided doses. The patient was found in bed unconscious, with vomited matters over his surroundings, after some hours became sensible, relapsed an hour or two later into heavy sleep, was again roused, and while playing cards became aphasic, deaf to conversation, acutely sensitive to other sounds, and finally died of hemiplegic apoplexy. It is plain that the wormseed was not the direct immediate cause of all these symptoms or of the fatal result.

tables. It has a neutral reaction, but unites with alkalies to form salts, and hence is freely soluble in alkaline solutions.

PHYSIOLOGICAL ACTION.—*Absorption and Elimination.*—Santonin is only feebly irritant. It is absorbed readily, probably as a sodium santoninate, and by its elimination produces a very pronounced reddish discoloration of the urine, which is characteristic of the poisoning.

The color of the urine is a very marked yellow, which has at first an orange tint, but after very large doses becomes saffron-like, or sometimes even a purplish red, which has given origin to the idea that blood was present in it. According to Manns,[6] the addition of an alkali to the yellow urine causes it to become red.

The exact form in which santonin is thown off is not established, but probably it undergoes oxidation in the system. Kletzinsky asserts that the drug receives in the system six atoms of oxygen.*

General Effects.—The first and most characteristic symptom produced by large doses of santonin is xanthopsia, or yellow vision.

Xanthopsia was first noticed by Calloud. Usually it consists of a very deep yellow tint imparted to the landscape and to every object looked at,—an effect perhaps most comparable to that of looking through yellow glass; sometimes this yellow is replaced by green; and Heydloff states that he has seen patients in whom the tint was red, and others in whom it was blue. E. Rose[7] has published exceedingly elaborate papers upon this chromatopsia. According to Knies, the xanthopsia is preceded by transient violet vision.

In poisoning by santonin great pallor of surface, with a blue color around the eyes or involving the whole countenance, has been generally an early symptom; vomiting has not rarely been present, and sometimes has been accompanied by colicky pains. Besides these manifestations, giddiness, mental apathy or stupor, great coldness of the surface, profuse sweating, trembling, mydriasis, and finally loss of consciousness, with convulsions, often violent and accompanied by opisthotonos and emprosthotonos, and failure of respiration, are the usual phenomena of santonin-poisoning. The circulation seems to be very little affected.†

According to Fröhner, moderate doses of santonin produce in domestic animals polyuria, sometimes strangury, and very commonly so pronounced sexual excitement as to suggest that the drug may have value as an aphrodisiac. The toxic dose causes in dogs and other domestic animals accelerated breathing, slowing of the pulse, universal trembling, cramps, free salivation, unconsciousness, convul-

* Chrysophanic acid produces a discoloration of the urine similar to that caused by santonin. According to Hoppe-Seyler, the cause of the coloration can readily be distinguished by adding caustic soda to the urine, and then shaking up with amylic alcohol, when, if the coloration proceeds from santonin, the urine is decolorized, while, if it be due to chrysophanic acid, the alcohol takes up only traces of the coloring-matter.

† Case, *Arch. für Exper. Path. und Pharm.*, vi. 302.

sions, dilated pupils, and death.* After death the lesions are not absolutely constant, but hyperæmia of the nerve-centres and congestion of the lungs and heart are nearly always present.

Santonin must have a powerful action upon the nervous system, but we have no detailed knowledge as to its general physiological action. Knies† believes that the chromatopsia depends upon a peripheric action of the drug which checks the response of the retinal elements first to the violet and later to the red end of the spectrum. The yellow vision of jaundice is an analogous phenomenon, caused, according to Knies, not by the staining of the ocular tissues, but by a toxic effect on the retina. Santonin often increases the flow of urine, and, according to Farquharson,[8] it also increases slightly the elimination of urea.

THERAPEUTICS.—Santonin was introduced into therapeutic use in 1830 almost simultaneously by Alms and by Kahler, and is one of the most reliable remedies that we have in the treatment of the lumbricoid or round-worm. Von Schröder[9] believes that he has proved by direct experiment that santonin is feebly toxic to the round-worm; but in this he is in opposition to the general clinical experience and the almost universal belief of helminthologists that santonin acts directly upon the intestinal parasite. It certainly is a very efficient remedy, but it should either be combined with or followed in about two or three hours by a brisk cathartic. The combination of calomel and santonin has been much commended.

As long ago as 1862 Guépin and Martin[10] recommended santonin in *amaurosis*, asserting it to be especially useful in those cases in which there had been choroiditis and iritis. These statements have been confirmed by D. Dyce Brown,[11] as well as by Ogston. G. Frank Lydston affirms that santonin is a valuable remedy in *epilepsy*. D. H. Bergey[12] asserts that santonin has especial relations with the uterus, and, if given in full dose at the time of the molimen, is an efficient remedy in *acute suppression of the menses*.

TOXICOLOGY.—There was at one time a tendency in the profession to attribute the toxic symptoms caused by santonin medicinally given to contaminating strychnine. The incorrectness of this has been demonstrated by Krauss and others. The following cases are instructive:

A child five years old was killed in half an hour by an unknown quantity,[13] and one six or seven years old is said to have been destroyed by six grains of the acid, after suffering from hæmaturia:[14]‡ four grains produced very serious symptoms in a child four years old.[15] In Grimm's[16] case, a rather feeble child five years old took two one-grain doses of santonin, and was seized with convulsive tremblings, which increased in severity until they became severe convulsions, accompanied by uncon-

* See experiments of Manns (*Das Santonin*, Marburg, 1851), of Rose (*Virchow's Archiv*, 1859, xvi.), of T. Krauss (*Inaug. Diss.*, Tübingen, 1869), and of Fröhner (*Monatshefte f. Thierheilk.*, 1893, iv.).

† Knies, *The Eye in General Diseases*, William Wood & Co., New York, 1895.

‡ This is probably a mistaken observation, the urine being only blood-colored, and not containing blood (see page 791).

sciousness, trismus, pallor of the face, cold sweats, dilated pupils, and rapid pulse and respiration. Thirteen or fourteen hours after the ingestion of the poison, while the patient lay on her back, quiet, unconscious, with moderately dilated pupils and a slow, feeble pulse, death occurred suddenly. Nine-tenths of a grain of santonin are said to have caused complete unconsciousness in a child five years old.[17] Six grains of santonin caused in a child five years old epileptiform convulsions and death in thirty-five minutes (W. J. Kilner[18]). One grain and a half produced in a child three and a half years old symptoms of the utmost severity, not reaching their maximum until two days after the ingestion of the poison:[19] for other cases, see C. Bevill.[20] In one case complete blindness persisted for nearly a week.

It is a curious fact that some of the text-books advise the use of santonin in doses larger than those which have produced serious or even fatal poisoning. Very alarming symptoms have been occasioned by two one-grain doses exhibited within three hours in a child eight years old (Grimm); in a child two and a half years old, four grains apparently came very near causing death (Berg[21]); and in the fatal case noted on page 792, only two grains were taken by a child five years old. The reason large doses have been so often given with impunity is the great insolubility of the crystals of the drug. The treatment of poisoning by santonin, after evacuation of the stomach and bowels, must at present be entirely tentative. One case appears to have been saved by artificial respiration; but Binz[22] has found amyl nitrite, morphine, and artificial respiration alike useless in animals: chloral given before the poison appeared to be of service.

ADMINISTRATION.—Santonin is best administered in troches, which should always be made of the unpowdered drug, so that the slow solution of the santonin in the intestine shall produce the greatest possible effect upon the worm with the least absorption of the remedy. The dose for an adult is two to four grains (0.13–0.26 Gm.); for a child two years old, one-quarter to one-half a grain (0.016–0.03 Gm.). For young infants, santonin is hardly a safe remedy in any efficient dose. When a dose of any size is given, it should not be repeated in less than eight hours, and the last dose should be accompanied by a purgative amount of calomel.

The soluble *sodium santoninate* is much more dangerous and less efficient than santonin: the object is to get as much of the remedy as possible in contact with the worm, and, as in order to do this a slow, not a rapid, absorption is necessary, the insolubility of santonin is an advantage.

ASPIDIUM. U. S.—*Filix Mas*, or *Male Fern*, is the rhizome of Dryopteris filix mas, or male fern of Europe. Under the name of Aspidium* the present U. S. Pharmacopœia recognizes both it and the rhizome of

* It is probable that many species of the genus Aspidium are active. Poulsson (*Arch. f. Exper. Path. u. Pharm.*, 1895, xxxv.) separated from the rhizome of Aspidium spinulosum two acids closely allied to filicic acid, a yellow and a white *polystichic acid*; and both he and Valter Laurén have found these extracts of the plant to be active tæniacides.

the indigenous D. marginale. The rhizome, when perfect, is from six to twelve inches long, and covered with large, brown, imbricated scales. Its taste is bitter and astringent.

Aspidium contains an amorphous acid, *filicic*,* which, according to the experiments of E. Poulsson,[23] is a very active substance, causing, in the frog, at first excitement and then paralysis of the central nervous system, and finally paralyzing the heart and exerting a marked influence upon the muscles: producing in warm-blooded animals violent diarrhœa, with a general paralysis due to depression of the spinal centres, and finally cardiac palsy. Kobert,[24] however, as the result of his experiments, believes that the vermifuge principles of male fern do not depend solely or even chiefly upon filicic acid, but upon the ethereal oil.

The official oleoresin (OLEORESINA ASPIDII, U. S.) thoroughly represents the crude drug. It is a dark, thick liquid, of a bitter, nauseous, slightly acrid taste. In overdose it is a violent poison, producing excessive vomiting and purging, with general weakness, tremors, cramps in the extremities, increased reflexes, amaurosis, and finally, in some cases, violent tetanic convulsions, with opisthotonos, stupor deepening into coma, and collapse. Icterus is sometimes apparent. Eight grammes of the extract have caused death in a child about three years old; six drachms of the oleoresin have several times proved fatal in the adult:† in Paltauf's[25] case the fatal result is said to have been due to four and a half grammes. Disturbance of the special senses is a not infrequent symptom in aspidium-poisoning. Deafness without loss of vision has been noted (case of Grant[26]). More commonly amblyopia or complete amaurosis occurs. One or both eyes may be affected, and total blindness, with gray atrophy, may remain as a permanent condition (Katayama and Okamoto;[27] also Bayer[28]). Experiments upon dogs indicate that the primary influence of the drug is on the ganglion cells of the retina. Fröhner[29] has noted after death, in the lower animals, hemorrhagic gastro-enteritis and cystitis, with violent parenchymatous nephritis. According to Quirll (quoted by Eich), the fatal result is due partially to violent irritation of the gastro-intestinal tract and partially to an influence upon the nerve-centres.

THERAPEUTICS.—Male fern is employed almost exclusively against the *tapeworm*. In its administration it is necessary to regard strictly the general rules applying with greater or less force to all anthelmintics, but which are especially imperative when a drug is employed against the tapeworm. The patient should live upon milk and a little bread for one day, and the following morning take a full dose—one half to one fluidrachm (2–4 C.c.)—of the oleoresin, fasting, and repeating it in two or

* Aspidin of R. Boehm (*Archiv f. Exper. Path. u. Pharm.*, 1896, xxxviii.) is distinct from filicic acid, and although poisonous both to frogs and to higher animals, appears not to be an active tæniacide.

† *Therap. Monatsch.*, 1889, iii.; *München. Med. Wochen.*, 1890, xxxvii.; *Lancet*, 1882; *Deutsch. Med. Wochen.*, 1891, xvii.

three hours. At noon the patient may eat freely, and in the evening a brisk cathartic should be given.

PEPO. U. S.—*Pumpkin Seed.*—The seeds of the ordinary pumpkin are a most valuable remedy in cases of *tapeworm*, perhaps even more efficient than the male fern, and perfectly harmless. Two ounces (62 Gm.) of the seeds may be beaten up with sugar into an electuary, or with water into an emulsion, and be taken fasting in the morning, the patient having dieted the previous day. Some hours after their administration a brisk purge should be given. I. G. Wolff asserts that the active principle is a resin, which he has found efficient in doses of fifteen grains (1 Gm.).

TURPENTINE, in doses of half a fluidounce, has been used in cases both of *tapeworm* and of *round-worm*. It is efficient, but is liable to produce unpleasant effects, and should be employed only when other remedies have been used without success or are not to be had. It should be given in combination with twice its bulk of castor oil, or sometimes in smaller doses as an aid to other vermifuges.

GRANATUM. U. S.—*Pomegranate Rind.*—The bark of the pomegranate root is efficient, though very unpalatable, against the *tapeworm*. The decoction of the fresh root (two ounces to one pint) is to be preferred; a pint of it to be taken in three doses, an hour apart, before breakfast. C. Tanret[30] has isolated from the bark four alkaloids, of which two, *pelletierine* and *isopelletierine*, have been found by Dujardin-Beaumetz to be active tæniacides. It is stated that in sufficient amount they act in the same manner upon the higher animals as does curare, causing paralysis of the motor nerves, without affecting sensation or muscular contractility. The dose of the salts of the alkaloids is said to be 4.6 grains (0.3 Gm.). G. Coronedi[31] agrees with the statement that the paralysis is peripheral, but believes that the muscles themselves are affected. The efficiency of pelletierine as an anthelmintic has been confirmed by various clinicians. It has by some been used in doses of twenty grains (1.3 gm.). Dujardin-Beaumetz also has employed it successfully in *Ménière's disease*, and states that hypodermic injections of six grains produce in man severe vertigo and muscular weakness, with great retinal congestion. We have seen five grains cause in the adult pronounced muscular weakness amounting almost to general paralysis, and a number of cases have been reported in which it has produced in infants symptoms so severe as to discourage its employment in patients of that class.* Galezowski[32] has used pelletierine in paralysis of the third and sixth pairs of nerves with asserted good results.

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* See *Bull. de Thérap.*, lxxviii., lxxix., lxxx., cxi., July, 1886; also *University Med. Magazine*, i. 639.

THYMOL, U. S., has been used by Neuma Campi * for the destruction of *tapeworm:* he gives half an ounce of castor oil in the evening, in the morning two drachms (7 Gm.) of thymol divided into twelve doses, one to be taken every quarter of an hour, and twenty minutes after the last dose of thymol another dose of castor oil. F. M. Sandwith [33] confirms the statement of Federici that thymol acts with extraordinary power upon the *Ankylostoma duodenale*, the cause of the so-called *tropical anæmia* of Egypt and elsewhere. He gives it in thirty-grain doses, repeated in twenty-four hours; the result being usually great giddiness, lowering of the temperature from 1° to 2° C., slowing of the pulse and respiration, staggering, and sometimes even collapse.

KAMALA. U. S.—*Kamala.*—The glands and hairs from the capsules of Mallotus philippinensis, a plant cultivated in India as a dye-stuff. It is said to be an efficient parasiticide in cases of *tapeworm.* It is an orange-red, very inflammable, granular powder, mixing with water with some difficulty, and containing traces of a volatile oil and coloring resinoids, to one of which Anderson has given the name of *Rottlerin.* Kamala, in full doses, is actively purgative, indeed drastic, and sometimes causes also nausea and vomiting. It imparts its virtues to alcohol, and hence may be exhibited in the form of tincture. The dose of the powder is from one to two drachms (4–8 Gm.) suspended in syrup, given in the morning, and repeated in eight or ten hours if it do not purge.

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FAMILY III.—DIGESTANTS.

IN this family are associated a few remedies which are used to aid the alimentary canal in dissolving the various articles of food.

PEPSIN.

As is well known, there is secreted by the gastric glands a peculiar albuminous body, which has the power not only of coagulating albumin, but also, with the aid of acidulated water, of redissolving it. To this principle the name of pepsin has long been given. A discussion of its nature and properties would be more in place in a work on physiology than in one on therapeutics. The U. S. Pharmacopœia now recognizes a stronger and weaker pepsin. PEPSINUM, U. S., or *Pepsin*, is required by the Pharmacopœia to be able to digest three thousand times its weight of freshly coagulated egg albumin. PEPSINUM SACCHARATUM, U. S., or *Saccharated Pepsin*, contains ninety per cent. of sugar of milk, and should be able to digest three hundred times its weight of egg albumin.

The dried stomach of calves has been used from time immemorial for the purpose of coagulating milk, by housewives, with whom it is customary to place the dried viscus in wine, and to call the liquid thus formed, as well as the prepared stomach, *rennet*. It is stated by James Gray[1] that rennet-wine should be of such strength that one teaspoonful of it will coagulate a pint of milk. Rennet is said to have been long employed in England as a domestic remedy in dyspepsia.[2] In South America the inner coat of the gizzard of the ostrich is stated to be put to a similar use (E. S. Wayne[3]), and in our own country the dried gizzards of chickens and turkeys are no less famous among medically inclined housewives.

Various processes have been suggested for the preparation of the drug, but none of them yields a pure proximate principle, if indeed pepsin have really such nature and be not an albuminous body of varying constitution.

Whatever form of pepsin be used, if good effects are to be obtained from it it must be given with acid, unless indeed there be reason to believe that this constituent of the gastric juice is not wanting. Alcohol destroys the digesting power of pepsin, and therefore wines are inferior preparations of it. The reactions of pepsin with organic and inorganic matters are very complex, and not well understood: consequently we think the physician should eschew all elixirs or compound preparations

of the drug, using only the powdered pepsin or a glycerole of pepsin, or a freshly prepared digestive solution of water and muriatic acid, or glycerin, water, and muriatic acid. If other remedies are to be given it is no great hardship to write a second prescription for them.

THERAPEUTICS.—It is a question of some importance to decide how far pepsin is valuable and reliable as a medicine. It is evident that any influence for good which it possesses is dependent upon its solvent power, and that this, therefore, is a measure of its value. Only a small portion of commercial pepsin approximates in power the official standard. Moreover, the pepsin in life must soon pass out of the stomach. One of two conclusions seems to be inevitable: either the doses of pepsin habitually used are preposterously small or else pepsin acts upon the stomach itself in some way as a stimulant. Clinically, pepsin has been used with asserted advantage in the *loss of digestive power* in adults, whether primary or occurring in the course of other affections. Probably four-fifths of the drug which has been given has been inert, either originally or from the method of its administration; and in the great majority of cases the good that has been achieved has been due, not to the pepsin, but to the regulation of the diet and habits of the patient and to the drugs which have been exhibited along with the animal ferment. The value of pepsin has been overestimated, and it has been given to adults in ridiculously small doses: at least half a drachm (2 Gm.) of the ordinary commercial article, or of the *Saccharated Pepsin*, U. S., should be exhibited at a dose. The testimony as to the usefulness of pepsin in diseases of young children is very strong. To such it is generally given in doses proportionately much larger than those usually exhibited to adults. The use of small doses of pepsin in children is therefore much more rational than in adults; and our own experience is in close accord with what seems to us the dictates of common sense: in the *chronic indigestion* and consequent *diarrhœa* of young children it may be tried with great hope of benefit. To a baby six months old five grains (0.3 Gm.) of the saccharated pepsin may be given in a little acidulated water after each feeding. Pepsin (U. S.) given in doses of ten to fifteen grains (0.7–1 Gm.) to the adult probably has some digestive value.

PANCREATIN, U. S., has been extensively used in *dyspepsia* as a digestant in lieu of pepsin. For action it requires the presence of an alkali, and in the acid gastric juice would not only not act, but would itself in all probability be digested and destroyed as a ferment;[4] and it is of no value except for the preparation of predigested foods.

EXTRACTUM MALTI.

Malt is the seeds of the ordinary barley caused to enter the incipient stage of germination by artificial means and dried. It is prepared by soaking the grains in water and leaving them in heaps in a room of moderate

temperature, and by occasional turning preventing the heat given off during the process of germination from accumulating; then finally killing the germ with heat. The color varies from pale amber to black, according to the degree of the heat used in drying. There is formed during germination a peculiar ferment, *diastase*, one part of which is able to convert about two thousand parts of starch into dextrin and glucose. The EXTRACTUM MALTI of the U. S. Pharmacopœia is made by rapidly evaporating an infusion of malt to the consistency of a thick, honey-like liquid at a temperature not above 130° F. It should contain practically all the diastase of the malt. The odor of the extract of malt is slight and peculiar, the taste sweet, and the reaction to paper distinctly acid. It dissolves freely in water, and is precipitated by alcohol, tannic acid, mercuric chloride, and various other metallic salts. Commercial malt extracts vary greatly: some of them are practically preparations of glucose, others are of the nature of strong or weak beers. True extract of malt contains no alcohol at all. Extract of malt has been much used in cases of disease with failing nutrition, and especially when the power of digesting substances is feeble. When it contains largely either glucose or alcohol it affords food-material to the system; but the important question for the therapeutist is, How far is it possible in disease to aid in the digestion of starchy substances in the stomach and intestines by the use of diastase? R. H. Chittenden and G. W. Cummins have made a series of investigations in order to determine the conditions which are necessary for the amylolytic action of diastase. They find that it acts better in a neutral than in an alkaline solution; that proteid matters when present in the alkaline solution prevent the retarding influence of an alkaline carbonate; that neutral peptone exerts a direct stimulant effect on the amylolytic action, but that the greatest amylolytic action is observed in the presence of proteid matter partially saturated with acid, although a larger percentage of acid-proteids may cause complete destruction of the ferment. These results seem to prove that diastase, when taken into the stomach, must sooner or later be completely destroyed by the gastric juice, and that in order for it to have any distinct effect upon digestion it must be given at the beginning of the meal. In *cancer* of the stomach and other diseases in which the gastric juices lack acidity, the action of diastase upon starch must be more pronounced; but unfortunately the failure of the starch-digestion is usually associated with gastric hyperacidity.

PAPAIN.

The Carica Papaya is an herbaceous tree universally cultivated in tropical countries for its fruit, the papaw, the juice of which yields a peculiar ferment, to which the name of *Papain* was given by Wurtz, but which is now generally known by the name originated by Pekolt, *Papayotin*. This substance is a ferment, which has the power of dissolving fibrin, muscular fibres, tissues, etc.

According to Wurtz, one part of papain in alkaline solution at a temperature of 40° C. is capable of dissolving one hundred and seventy-five parts of moist fibrin, which it converts into a peptone. Wurtz affirms that it makes no difference whether the solvent solution be alkaline or acid, but Brunton, Wyatt, and Martin state that as little as one-half per cent. of hydrochloric acid arrests the digestion. Albrecht, however, reaffirms that hydrochloric acid hastens the action of papain, and states that the official preparation in use in the Paris hospitals is an acid one. Further, in an elaborate series of experiments, August Hirschler[5] reaches the result that digestion goes on most rapidly in acid solutions, that it is very feeble in alkaline solutions, and ceases entirely when the alkalinity becomes excessive. It is stated that in order to convert fibrin entirely into pure peptone, so that nitric acid will produce no precipitate, the proportion of the ferment must be at least three per cent., and the digestion must continue for forty-eight hours.

Papain first coagulates milk, then precipitates it, and finally digests it into a thin fluid. Taken into the stomach, papain has no action upon the living tissues, but one grain of it injected directly into the blood is sufficient to cause death in a very short time in rabbits or in dogs. Its action on albuminoids is said to resemble that of trypsin rather than that of pepsin. (See Martin.[6])

Papain has been used in medicine as a substitute for pepsin, in doses of five to ten grains (0.3–0.6 Gm.). It has also been very highly recommended for the purpose of destroying organic tissues of low type, as in *diphtheria* (A. Jacobi[7]), in the thickening of chronic *eczema*, in *warts*, and in *pyogenic membranes* surrounding old sinuses or abscesses. It is not caustic, but simply dissolves the diseased tissues, and is said to cause no pain.[8] It should be applied, one part each of papain, glycerin, and water. In our laboratory experiments commercial papain of the most esteemed brands has failed to exert any solvent power over albuminous substances, and it is probably a remedy of little value.

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FAMILY IV.—ABSORBENTS.

THIS class contains remedies which are used for the purpose of absorbing acrid and deleterious materials, such as offensive discharges on the exterior of the body, and acrid secretions, or the irritant products of the partial decomposition of food, in the alimentary canal. For the first purpose very fine dry earth and plaster of Paris are used to some extent in practice; but, as their employment is purely within the province of the surgeon, we shall say no more about them here.

CHARCOAL.

Charcoal is official in the U. S. Pharmacopœia in two forms:

CARBO LIGNI.—*Charcoal* prepared from wood.

CARBO ANIMALIS.—*Animal Charcoal*, prepared from bone.

Charcoal for medicinal purposes should be made out of a light, porous wood: that prepared from the young shoots of the willow or of the poplar is almost exclusively employed. It is a black, brittle substance, and should have more or less lustre. It has a very remarkable power of absorbing many times its own bulk of gases, and, when exposed to the air, increases rapidly in weight. It should therefore, when intended for medicinal purposes, be powdered as soon as it is burnt, and put in small, completely filled, closely sealed bottles.

Animal charcoal, or *bone-black*, formed as it is by the partial burning of bones, contains a large percentage of calcium phosphate and carbonate. *Purified Animal Charcoal* (CARBO ANIMALIS PURIFICATUS, U. S.) is prepared by removing the lime salts by dilute muriatic acid.

THERAPEUTICS.—Internally, charcoal is employed as an absorbent in fermentative intestinal *dyspepsia*, *cardialgia*, and similar disorders. As moist charcoal is not an absorbent, it is evident that it is of very little value; its habitual employment is generally combined with that of laxatives for fear of accumulation in the alimentary canal. Dose of charcoal from one to two drachms (4–8 Gm.). Except in a mechanical way, it is perfectly innocuous in any dose.

FAMILY V.—DISINFECTANTS.

DISINFECTANTS are substances which are used for the prevention of the development, or for the destruction after development, of disease-germs. When these disease-germs arise solely without the human body, as is the case with miasmatic and probably also yellow fever, we have at present no direct power over their growth ; the only thing that can be done is to alter the conditions favorable to their production. Thus, in the case of intermittent fever, by drainage, by the planting of eucalyptus trees, or perhaps by other measures, swampy lands may be made so dry that the malarial organisms will not develop in them ; whilst in the case of yellow fever, whose germs appear to require for their growth mixed animal and vegetable matter in processes of decay at high temperature, by the destruction or removal of such matter—that is, by cleanliness—the development of the germs may be more or less controlled.

An *antiseptic* is not always a *germicide*, though a germicide is always an antiseptic. The antiseptic is a substance which has the power of preventing putrefaction,—that is, the growth of the organisms which produce putrefaction ; whereas the germicide is a substance which is capable of killing disease-germs and their spores, which entities are much more resistant than are the bacteria of putrefaction : thus, alcohol, common salt, borax, ferrous sulphate, and many other agents commonly used as antiseptics do not, even in concentrated solution, destroy the spores of bacilli, and consequently are not germicides.

The more imperfectly developed animal organisms are the more tenacious are they of life ; all substances actively poisonous to contagions are still more poisonous to the germinal matter of human beings, so that it is impossible to destroy the contagion-germs in the confined air of a room containing people. When it comes to the general atmosphere, to attempt to disinfect it, to essay the destruction of a wide-spread poison, such as, for example, exists in a small-pox epidemic, is childish.

So long as a patient must remain in the room, the best that can be done is to disperse the germs by admitting or forcing in large quantities of *fresh* or *pure air*. In ventilating, it is not merely air, but pure air, that is required. To ventilate one room into another, as is sometimes done, is foolishness ; to open a window with the wind blowing over a miasmatic swamp or an open sewer may be but to invite disease. The opportunity to destroy disease-germs is to be found not after they have been dispersed into the air, but while they are still in connection with the various

solids and fluids passed from the body or brought in contact with it. In most, if not all, contagious diseases the poison-germs are eliminated in large quantities with the urinary and fecal discharges ; it is of vital importance to act on the excretions as soon as they leave the body, and the disinfectant should be placed in the receptacle *before*, not after, it is used. Moreover, the discharges should be allowed to stand mixed with concentrated germicide until sufficient time has elapsed for it to kill the organisms. Chambers and other receptacles should therefore not be immediately emptied after use. To allow any excretion, sputum, or other infected discharge to exist for a moment undisturbed is most culpable neglect. *Spit-cups, urinals*, etc., *should therefore have the disinfectant in them whilst waiting for use.*

It is plain that the practical problems of disinfection may readily be grouped under three headings : first, the treatment of filth which is not infected ; second, the treatment of infected filth ; third, the use of germicidal substances upon the human body to prevent or overcome infection.

For the purpose of convenience we shall divide the present chapter into two parts : first, the consideration of the problems of disinfection which are connected with filth outside of the body ; second, the consideration of methods of destroying germs in or about the human body.

FILTH.

The one protective against filth is cleanliness,—that is, the removal and dispersion of the filth, so that it may be destroyed by natural or artificial methods, or be so placed that it can do no harm. It is plain that for the destruction of waste material antiseptics are worse than useless, they having a tendency to preserve dead organic matter and not to destroy it, and unless the filth has been already infected, germicides are of no value. In the case of infected filth it is essential that it be destroyed rapidly by fire, or that *by the use of germicides it be rendered innocuous before dispersion.*

The most complete and the most destructive of all disinfectants is fire. When circumstances favor its use it simply ends the whole matter, whether the filth be or be not infected. For the purposes of destroying uninfected filth artificially there are various substances which are capable of causing oxidation. The practical efficiency of any agent is, however, a question not simply of power, but of power as contrasted with cost, so that there are in reality only a few substances which can be used for destroying filth. For the purification of water the so-called filtration beds can be made absolutely effective. They destroy organic matter not by any process of filtration, but by chemical disintegration caused by the immense masses of lower organisms growing in them. The drugs which are capable of use as practical destroyers of organic matter are certain metallic salts, lime, chlorinated lime. Some, but not all, of these substances are active germicides.

ZINC—LEAD—IRON.

There are various metallic salts which are capable of taking sulphur away from sulphuretted hydrogen and other gases, and have therefore been used as disinfectants. Among these may be mentioned *zinc sulphate* and *chloride* and *lead nitrate*, a solution of the latter salt having been especially employed under the name of *Ledoyen's Disinfectant Solution*. Such disinfectants, however, are little more than deodorants, and, although much exploited, are of little value, and capable of doing much harm by creating a false security.

The oxidizing power of iron oxides led at one time to their use for the purposes of purification of water. The method, however, has been thrown into complete desuetude by the immense superiority of the processes of purification by filtration. *Copperas*, or impure *ferrous sulphate*, is, however, still occasionally employed for the purification of cesspools and similar receptacles.*

The changes wrought by ferrous sulphate thrown into a mass of decomposing matter are very complex and not absolutely known. In the first place, if sulphuretted hydrogen and ammonia are present, an iron sulphide is at once precipitated: again, a part of the salt is decomposed by the ammonia, and probably also by the stinking alkaloids which exist in the decomposing mass of a cesspool ; further, by oxidation, in all probability, some of the ferrous oxide is changed into the sesquioxide, by which the ozonizing power of an iron compound is doubtless exerted long after the destruction of the original salt. The sulphuric acid set free from the iron very probably takes part to a feeble extent in the destructive reactions which are set up. From what has been already stated, it is evident that the sole use of the copperas is in altering the course of putrefaction and in destroying its products.

If a rapid effect is desired, or if a mass of solid material is to be acted on, the copperas should be in solution ; if a more persistent action is wanted, or if the mass is liquid, the method employed by Eckstein, of using a parchment sack, may be resorted to, or the salt in powder may be scattered over the surface of the material to be disinfected. The power of any metallic salt to oxidize and destroy organic matter is, however, very feeble, and the germicidal power of copperas very slight; so

* That this substance has some value for use in cesspools, etc., is indicated by the experiments of Albert Eckstein, who published (*Zeitschrift des Oester. Apotheker-Vereines*, Feb. 10, 1873) an account of his attempts to disinfect a privy which was used daily by one hundred persons: 1. Two pounds of the ferrous sulphate in solution were used. After from two to three hours all bad smell had disappeared, but in twelve hours all the influence of the disinfectant was lost. 2. The cupric sulphate was employed in solution; result the same. 3. Two pounds of the ferrous sulphate in crystals were thrown in; their effects lasted two days. 4. The cupric sulphate, the same. 5. Sulphurous acid in solution rapidly lost its effect, and was exceedingly irritating to the respiratory organs. 6. Two pounds of impure carbolic acid filled the house for two days with so disagreeable a smell that it was impossible to tell whether the original odor was destroyed or covered up. 7. Two pounds of ferrous sulphate in a parchment sack exerted a disinfecting influence for three full days, and when the parchment sack was drawn up it contained only some dirty, odorless fluid. 8. Two pounds of the best chlorinated lime in the parchment sack disinfected the privy for at least nine days.

that the chief action of copperas, as of other metallic salts, is as a deodorant rather than as a true disinfectant.

LIME is probably the oldest of all the disinfectants, but is of value only as a destructive agent,—*i.e.*, as causing a slow oxidation of organic matter. It is notorious that a compost heap to which lime has been added rots—*i.e.*, oxidizes—much more rapidly than one which has none of the alkaline earth in it. This action of lime is, however, too slow for ordinary purposes; moreover, there are objections to the use of lime as a disinfectant.

The poisonous principles contained in sewage, etc., whatever their nature may be, are probably volatile, and lime, acting as a strong base, sets free large quantities of ammonia in animal matter undergoing decomposition. It may be that volatile poisons—alkaloids—are liberated with the ammonia; but whether they are or not, it is a well-known physical fact that a volatile substance in escaping carries off with it even non-volatile materials, and facilitates to a still greater degree the escape of principles less volatile than itself.

Lime is, for the above reasons, not available for use as a disinfectant in cesspools and sewers unless it is added in large quantities day by day from the beginning, so as to keep the collection under its influence, or unless some absorbent is added with it to take up volatile principles. In the ordinary open privies of the country, a shovelful of a mixture of lime and plaster of Paris, or of lime and dry earth, thrown in day by day, will tend to prevent odor, and at the same time will prepare the contents for use as manure.

When spread upon walls in the form of whitewash, lime may act to some extent as an oxidizer; but probably its chief influence is as an absorbent, which takes up the deleterious emanations.

A very striking illustration of this action of whitewash occurred some years since in the New York City Hospital. A ward which stood isolated from the remainder of the institution had been used for the reception of cases of typhus fever from the shipping of the port. It was finally abandoned and allowed to stand unoccupied, with its windows wide open, for several months. At the end of this time a gang of men was set to scraping the whitewash off the walls. Of these workmen a majority were seized with the ship-fever, and several died.

As a chemical destroyer of organic matter chlorinated lime is probably more effective than simple lime, but as it is also a powerful germicide, it is considered in the next group of disinfectants.

INFECTED MATERIALS.—When infected organic materials are of such character that their destruction is not desirable, the disease-germs which they contain may be killed by the use of moderate heat or of certain drugs.

Heat may be used as a germicide, either *moist* or *dry*. In the early part of the present century Henry, of Manchester, showed that the ac-

tivity of vaccine lymph is destroyed by moisture at 140° F. in four hours. Carsten and Coert have also proved that calf lymph is at once sterilized by boiling water. George N. Sternberg found that boiling water will quickly destroy the vitality of all organisms known as disease-germs. This accords with the experiments made with hot air in the laboratory of Koch, in which it was found that all bacteria are killed by an exposure of one hour and a half to the temperature of 212° F. with moisture. Similar results have also been arrived at by other experimenters, and we think it may be considered as established that non-spore-bearing infectious bacteria are destroyed by water or steam at a temperature of 212° F. The *spores* of the bacilli have, however, much greater powers of resistance. Sternberg found that boiling for two hours does not kill the spores of Bacillus subtilis, although a more prolonged boiling is fatal, but that steam at a temperature of 110° C. (230° F.) for one or two minutes, or 105° C. (220° F.) maintained for ten minutes, will infallibly kill the spores. If dry instead of moist heat be employed, a much higher degree of temperature will be required. In the experiments of Koch and his assistants with dry hot air, the spores of mildew required for their destruction exposure for an hour and a half to a temperature of 230° F., the spores of bacilli an exposure of three hours to a temperature of 204° F. All observers agree in stating that the addition of steam to dry air increases greatly its effect. Wolf[1] found that dry air at 140° C. was scarcely more destructive than watery vapor at 100° ; Koch, that five minutes' exposure to steam was equal to an hour or an hour and a half with the dried air. The results reached by Koch and Wolffhügel[2] are in accord with our other evidence, and may be considered correct. They are as follows :

1. A temperature of 100° C. (212° F.), dry heat, maintained for one hour and a half, will destroy bacteria which do not contain spores.

2. Spores of mould-fungi require for their destruction in hot dry air a temperature of from 110° to 115° C. (230°–239° F.) maintained for one hour and a half.

3. Bacillus-spores require for their destruction in hot air a temperature of 140° C. (284° F.) maintained for three hours.

4. In dry air the heat penetrates objects so slowly that small packages, such as pillows or small bundles of clothing, are not disinfected after an exposure of from three to four hours to a temperature of 140° C. (284° F.).

5. Exposure to a temperature of 140° C. (284° F.) in dry air for a period of three hours injures most objects requiring disinfection (clothing, bedding, etc.) to a greater or less degree.

George H. Rohé[3] found that rolls of blankets exposed in a chamber heated to 280° F. for three hours were very slightly affected in their interior. This is in strict accord with the teaching of Parsons and Klein,[4] of the London Local Governing Board, and of other observers. We think that the superiority of prolonged boiling over other methods

of application of heat is established. In the sick-room, objects which can be boiled without injury should, immediately after their infection, be gathered into a close bundle, enclosed in a sheet, and as soon as possible thrown into boiling water without opening. When pillows, bedding, or articles of furniture are seriously infected, they should be taken apart and exposed to heat and steam.

CHLORUM—CHLORINE.

Chlorine gas is official only in the form of the AQUA CHLORI, which is prepared by heating together black oxide of manganese and hydrochloric acid, and allowing the chlorine which is generated to pass through water until the latter is saturated. *Chlorine Water* is a greenish-yellow liquid, of a very sharp taste, and having a strong odor of chlorine. When chlorine is brought into contact with organic substances and moisture, it unites with the hydrogen of the water and liberates nascent oxygen, which rapidly oxidizes and destroys the organic compound. When chlorine comes in contact with sulphuretted oxygen, it removes its hydrogen and thereby destroys it. On account of its destructive action on organic matter, its being extremely obnoxious to animal life, and its comparative expensiveness, chlorine gas is at present never used to disinfect rooms, ships' holds, or similar places. Inspired in sufficient amount, chlorine gas produces, both in man and in the lower animals, narcotism, and finally death from paralysis of the respiratory centre.*

The germicidal influence of chlorine is very great. Fischer and Proskauer found that dried anthrax spores maintained their integrity for one hour when exposed to the action of a dry chlorine atmosphere containing 44.7 parts of chlorine in 100; but when the air and the spores were moist, one hour's exposure to an atmosphere containing four per cent. of chlorine produced complete disinfection. If the exposure was continued for three hours, one per cent. of chlorine was an efficient germicide; and if the spores were exposed for twenty-four hours, the effective proportion of chlorine could be still further reduced. In Sternberg's[5] experiments, six hours' exposure of vaccine lymph dried upon ivory points to an atmosphere containing 1 part of chlorine in 200 was sufficient to destroy the infective property of the lymph, while the bacteria of putrid urine were destroyed after six hours' exposure to an atmosphere containing 1 part of chlorine in 400. Klein[6] also found that after the compartment of a stable in which pigs had died of swine-plague had been thoroughly fumigated for six hours with chlorine, healthy animals could be placed therein with safety.

The result of all our knowledge upon the subject of the disinfectant properties of *chlorine*, *iodine*, and *bromine* has been summed up by George H. Rohé[7] as follows:

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* Consult *Arch. f. Exper. Path. u. Pharm.*, xiii.

1. Chlorine is an efficient disinfectant when present in the proportion of 1 part in 100, provided the air and the objects to be disinfected are in a moist state and the exposure continues for upwards of an hour.

2. Chlorine, when used in sufficient concentration to act as a trustworthy disinfectant, injures colored fabrics and wearing apparel.

3. Bromine is an efficient disinfectant in the proportion of 1 part in 500, provided the air be in a moist state and the exposure continues for upwards of three hours.

4. Iodine, in solution, is an efficient disinfectant in the proportion of 1 part in 500, the exposure continuing for two hours.

5. The use of chlorine, and in a greater degree of bromine, requires considerable experience in management: when carelessly handled they may cause inconvenient or even dangerous symptoms in persons using them; hence they are not suitable as disinfectants for popular use.

Internally, chlorine water has been used in various diseases, especially in malignant *typhus*, but at present is rarely if ever so employed. It is stated to be stimulant and tonic to the stomach, and is thought by some to have an especial influence upon the liver. It has been employed in *chronic hepatic affections;* the dose is half a fluidrachm to two fluidrachms (2–7 C.c.) in three or four fluidounces of water. Chlorine water is a powerful irritant, capable of producing severe inflammation of the skin or toxic *gastro-enteritis.* Properly diluted, it forms an excellent stimulant, disinfectant, detergent wash for *foul ulcers*, and may also be used as a gargle in *malignant sore throat.*

CALX CHLORATA—*Chlorinated Lime.* U. S.—*Bleaching-powder* is a grayish-white substance occurring in powder or friable lumps, having a hot, acrid, astringent taste, and an odor resembling that of chlorine. It is made by the action of chlorine upon calcium hydrate, or slaked lime, and should contain at least twenty-five per cent. of chlorine. It probably varies in its chemical constitution, but, according to the most recent views, is chiefly composed of the calcium hypochlorite and chloride. When exposed to the air it slowly evolves hypochlorous acid, which, being an unstable compound, undergoes spontaneous decomposition, and finally sets free fourteen-fifteenths of its chlorine. When an acid is added to chlorinated lime, the chlorine gas is rapidly evolved. If a specimen of bleaching-powder be very moist, it generally contains an over-proportion of the deliquescent calcium chloride, and is correspondingly unable to liberate chlorine.

The experiments of J. R. Duggan[8] indicate that the hypochlorites are among the very best of our practical germicides. He found that 0.25 of one per cent. (1 part to 400) of chlorine as hypochlorite is an effective germicide even when allowed to act for only two minutes; while 0.06 of one per cent. (6 parts to 10,000) will kill the spores of B. anthracis and B. subtilis in two hours.

Bleaching-powder usually contains from twenty-five to forty per cent. of available chlorine. For most purposes, a solution made with

1 part of this preparation to 100 parts of water is strong enough, for it will contain from 0.25 to 0.40 of one per cent. of chlorine as hypochlorite. As is stated above, the smaller of these quantities is sufficient to destroy spores almost instantly. There are very few purposes to which disinfectants are applied that are not fulfilled by this solution of 1 to 100 of bleaching-powder. It is not dangerously poisonous, is said not to injure clothing, bedding, etc., and is very cheap, since bleaching-powder is worth only about five cents per pound. *For the destruction of disease-germs in urine, fecal discharges, sputum, etc., a saturated solution of bleaching-powder appears to be in all respects the best disinfectant known: for the purification of cesspools, sewers, or similar receptacles, or of masses of infected filth, chlorinated lime stands at the head of known germicides.**

LIQUOR SODÆ CHLORATÆ. U. S.—*Solution of Chlorinated Soda*, or *Labarraque's Solution*, is made by triturating chlorinated lime with a solution of sodium carbonate. It is a greenish-yellow liquid, having a slight odor of chlorine and a sharp saline taste. It contains, among other substances, sodium hypochlorite, and possesses the therapeutic and disinfectant properties of the chlorinated compound. Owing to its liquid form, its comparative freedom from odor, and its depositing sodium

* There are not many affairs in life in which the public have been so superabundantly fleeced as in the matter of disinfection. A most extraordinary part of this swindling is the ease with which distinguished members of the medical profession have given certificates of efficiency and value to comparatively inert and extraordinarily expensive proprietary compounds. Oddly enough, the cat that has drawn the chestnuts out of the fire for avaricious manufacturers has not even had the sense to smell the odor of its own paws when burning! There is *no proprietary disinfectant* whose value corresponds with its selling price. The following table, taken from an article by A. W. Harlan, of Chicago, was compiled some years since, but is believed to be still practically correct: of course, in it one unit is used throughout. The cost represents the same germicidal power throughout.

Name.	Full Cost.
Corrosive sublimate	$0.00 9/10
Chlorine	.01 1/20
Copper sulphate	.01 7/20
Mercury biniodide	.02 1/2
Mineral acids	.03 1/5
Bromine	.08
Ammonia gas	.13 1/2
Chloroform	.14 1/2
Chromic acid	.15
Potassium chlorate	.16 1/2
Silver iodide	.20
Picric acid	.20 3/5
Iodine	.21 2/5
Silver nitrate	.22 1/2
Potassium permanganate	.30 1/5
Carbolic acid	.34 1/5
Benzoic acid	.56
Salicylic acid	.69
Osmic acid	4.62 9/10
Thymic acid	4.80
Anhydrous prussic acid	11.00

Name.	Full Cost.
Corrosive sublimate	$0.00 9/10
Little's sol. phenyl	13.00
Fifty per cent. chlor. zinc, Squibb's	35.00
Feuchtwanger's disinfectant	35.00
Phénol sodique (Hance Bros. & White)	51.00
Platt's chlorides	66.00
Girondin	80.00
Williamson's sanitary fluid	80.00
Bromo-chloralum	80.00
Blackman's disinfectant	96.00
Squibb's solution impure carbolic acid	112.50
Burchardt's disinfectant	182.50
Phénol sodique, French	255.00
Listerine	495.00

chloride on evaporation, it is the most elegant of all the chlorine preparations for use in the sick-room. Properly diluted, Labarraque's solution may be employed for all the therapeutic purposes for which chlorine water is used. The dose is half a fluidrachm to two fluidrachms (2–7 C.c.) in half a tumblerful to a tumblerful of water.

ACIDUM SULPHUROSUM—SULPHUROUS ACID. U.S.

A somewhat elaborate study of the action of the sulphites upon vertebrata has been made by Pfeiffer,[9] who finds that they are poisonous when in very large doses, but that the rapidity with which they are oxidized into the sulphate frequently brings about sudden recovery in the deepest condition of poisoning. In sufficient amount they are said to paralyze the blood-vessels, the heart, and the respiratory apparatus.

Sulphurous acid and its salts are most efficient in destroying the low forms of life which are connected with putrefaction and fermentation, and for this reason are preservatives of organic matters; they are also among the oldest of disinfectants, having been used as long ago as 1771; but recent experimental evidence indicates that they have not the great superiority which has been attributed to them.

According to the experiments of Sternberg, 1 volume of sulphurous acid gas in 100 volumes of air is sufficient to disinfect dry vaccine matter. As these experiments are in accord with older observations, they may be considered as correct.

According to Wernitz, the action of pepsin, of ptyalin, of invertin, and of diastase is prevented by the presence of an aqueous solution of SO_2 of 1 : 1317 to 1 : 8600 (by weight); while the action of myrosin and of emulsin is neutralized by 1 : 21,000. Wernitz further says that strips of woollen or cotton goods saturated with putrefactive matter are disinfected by exposure of from four to six hours to an atmosphere containing four per cent. of sulphurous acid gas. The very elaborate experiments of Koch, of Wolffhügel, and of Sternberg have shown, however, that when the infectious material contains spores sulphur dioxide is of very little efficiency.

Sulphurous acid may be produced very cheaply upon the large scale by the burning of sulphur, and its vapor when thrown with steam into the hold of a vessel mixes with the water of the vessel and with the condensing steam, and so penetrates into all the cracks and places where the disease-germs may have found resting-places. It does not readily undergo decomposition; its ordinary salts are germicidal, and it is still relied upon for the disinfection of infected ships. On the other hand, in an ordinary room it does not find water in which to dissolve; it is liable seriously to impair clothing, bedclothing, and other organic material of value; and as formerly made, by burning in a simple iron pot, it was ineffective: so that the purification of apartments by burning sulphur in the house has been entirely displaced by formaldehyde.

The sulphites and bisulphites have been largely employed to arrest or control fermentation, and are useful in saturated solution in various parasitic diseases of the skin.

CORROSIVE SUBLIMATE.

In 1870 John Dougall announced that corrosive sublimate 1 part in 6500 would kill spermatozoa, and 1 part in 6000 infusoria; the later researches of Koch, Jalan de la Croix, and Sternberg have more than confirmed this result, and shown that corrosive sublimate is one of the most powerful of known germicides. Micrococci and bacilli in active growth without spores are killed by solutions of 1 in 20,000, while solutions of 1 in 1000 will rapidly destroy the spores of B. anthracis and B. subtilis. Results contrary to these have, it is true, been obtained by Klein, of London, who asserts that a one per cent. solution of the mercuric chloride is no more a germicide than is vinegar; but the evidence to the contrary is so strong that it seems almost a certainty that there was some error in Klein's experiment. According to the detailed experiment of Koch, the spores of B. anthracis are absolutely incapable of germinating in a proteid solution if as little as 1 part of corrosive sublimate in 300,000 be present. Sternberg confirms the experiments of Koch, and it would theoretically appear that 1 part of corrosive sublimate in 100,000 is sufficient to destroy germs in a mass of filth, provided the filth is so situated that the corrosive sublimate will remain in contact with it for some time. It must be remembered, however, that corrosive sublimate is so readily decomposed by ammonia and other substances usually present in a mass of filth that it is not available for disinfectant purposes on a large scale; even when the amount of organic matter is small, the usefulness of corrosive sublimate is often destroyed by its chemical instability: thus, it should not be used for the destruction of germs in fecal discharges. A standard solution of 1 part in 1000 may be used for bedding, which can be soaked in it, for washing the floors and walls of infected apartments, and for disinfecting the hands of surgeons and gynæcologists; after the corrosive sublimate has done its work it should be removed by free washing with pure water. Even in the cases just spoken of corrosive sublimate is often inferior to formaldehyde.

FORMALDEHYDE.

Formaldehyde, *formyl* or *formol*, is a gaseous body, which is obtained by the oxidation of methylic alcohol at moderately high temperature, as by passing the vapors over red-hot metal or carbon. It readily dissolves in water and alcohol, forming a colorless fluid, having a peculiar odor and an exceedingly irritating taste.

Formalin is a forty per cent. aqueous solution of formaldehyde, protected by a trade-mark name: a similar forty per cent. solution is sold as formaldehyde. The fifty per cent. solution would be more convenient, but undergoes decomposition and becomes turbid upon standing. The physician in prescribing should order simple solution of formaldehyde to save the expense attaching to proprietary remedies.

PHYSIOLOGICAL ACTION.—*Local Action.—Absorption and Elimination.*—Formaldehyde is an intensely active local irritant, producing even

when in very minute amount in the air violent irritation of the respiratory mucous membrane, or, it may be, fatal pulmonary inflammation. It is a powerful germicide.* It is also a very active coagulant of albumin and gelatin when in at all concentrated form ; and when added to blood it causes an immediate coagulation, with a serum so strongly colored red as to suggest destruction of the red blood-corpuscles, though it may be that the color is due simply to the squeezing out of the corpuscles from the clot. According to Mosso and Paoletti,[10] however, when added in a very dilute form to an albuminous solution, formaldehyde not only does not coagulate the albumin, but so acts as to prevent the coagulation of albumin by heat. It is therefore capable of absorption, and the statements made that the urine passed by animals to which it is given even in moderate quantities is incapable of putrefaction indicate that it is not only absorbed, but also eliminated unchanged from the kidneys.

General Effects.—The immediate violent irritation produced by formaldehyde is so great as to forbid either accidental or purposive poisoning by it, and we know of no case in which it has caused in the human being symptoms other than those of local irritation. Its general influence upon the higher animals is feeble.

Trillat[11] states that sixty-six centigrammes of formalin per kilogramme given to the guinea-pig are not mortal, although the urine passed by the animal is incapable of putrefaction ; whilst the intravenous injection of thirty-eight centigrammes per kilogramme causes in the rabbit no pronounced symptoms. According to Mosso and Paoletti, fifty cubic centigrammes per kilogramme injected hypodermically produce in the dog severe poisoning, with fall of temperature, ending after many days in death ; the same amount given by the stomach causes in the dog violent convulsions, general rigidity, salivation, and in a short time death, preceded by stupor and unconsciousness.

The fact noted by Mosso and Paoletti, that formaldehyde produces less severe symptoms when given hypodermically than when taken by the stomach in the same dose, demonstrates that the symptoms caused by it are largely the outcome of its local action.

According to Mosso and Paoletti, small doses cause rise in the blood-pressure, probably as the result of peripheral contractions of the arteries; whilst toxic doses depress the circulation and so act upon the blood that on exposure it coagulates instantly, with the separation of a dark red serum.

The discovery by Trillat, in 1888, that formaldehyde is a powerful germicide has been abundantly confirmed. In activity it probably ranks close to corrosive sublimate.

In a tabulated statement of the results obtained by numerous observers, Marion[12] shows that 1 part of formaldehyde in 20,000 will kill most bacteria if the

* Formaldehyde also has a very powerful influence on various forms of organic matter: 1 part in 4000 completely decolorizes wine, precipitating extractive and coloring matters.

contact be prolonged; and it seems to be at present commonly thought that as a general germicide it is equal in power to corrosive sublimate. Some of the later reports, as those of K. Walker,[13] indicate, however, that its strength is less than that of corrosive sublimate, though very much greater than that of carbolic acid or any of the ordinary disinfectants used, its one per cent. solution destroying all pathogenetic spores within an hour. According to the experiments of Aronson and of Burkhard,[14] it not only is a germicide, but also has the power of destroying the toxins of diphtheria, of tetanus, and probably of other diseases.

THERAPEUTICS.—On account of the safety connected with its use, its activity, its permanence of constitution, and its lack of destructive action on vegetable and animal substances, formaldehyde is probably the most reliable and the most generally useful of all the germicides when it is not necessary to bring the agent in contact with the human body. It does not affect either the color or structure of clothing or other materials in common use. Its vapor, being of low specific gravity, mixes readily with the air, and penetrates loose fabrics much more deeply than does any other known germicide.

Using an apparatus invented by himself for the production of formaldehyde directly from methylic alcohol, Trillat found that it was possible completely to disinfect rooms and the furniture contained therein in six hours, by the consumption of from four to six litres of the alcohol for each three hundred cubic metres of the room. In 1895 Van Ermengen and E. Sugg[15] sterilized in a room books and other small objects containing the germs of diphtheria, tuberculosis, scarlet fever, smallpox, etc., by means of formaldehyde evaporated from its watery solution in such quantity that there was about the value of five cubic centimetres of formaldehyde in one litre of air, and in 1896 it was demonstrated by E. G. Horton[16] that infected books shut up in a closed space could be disinfected in fifteen minutes by the vapor of commercial formalin,—one cubic centimetre of the formalin to three hundred cubic centimetres or less of air,—and that the books were not in any way injured by the process. More recently there has been abundant confirmation as to the activity of formaldehyde, which, when properly used in a room with moistened air, fails only when the objects are so dense or in such mass that they cannot be penetrated.

In disinfecting an apartment, windows, doors, chimneys, ventilators, and similar openings should be tightly closed, whilst the air should be made to contain at least one per cent. of formaldehyde gas, and at the end of twenty-four hours, when the apartment may be opened, should still be strongly impregnated. The gas may be obtained by the pulverization of formalin or other solution of formaldehyde, but not by the simple evaporation of the solution, since the formaldehyde, upon the application of heat, becomes largely polymerized into a solid, *paraform*, which gives off formaldehyde slowly and in small quantities. It is stated that the addition of glycerin to the solution of formaldehyde prevents the polymerization by heat of the formaldehyde, so that the so-called *glycoformalin* (formaldehyde thirty parts, water sixty parts, glycerin ten parts) is preferable to the watery solution, although its use has the distinct disadvantage of leaving many articles in the room sticky from a coating of glycerin.

Notwithstanding the convenience of the solutions of formaldehyde, the prices at which these solutions are sold and the ease with which formaldehyde is formed directly from methylic alcohol make the use of one of the various commercial formaldehyde lamps which produces the gas automatically much cheaper as well as probably more effective for the purposes of disinfecting on a large scale. By standing the lamp in a large iron pot, all possibility of danger from fire is avoided, and the apparatus, once charged and started in a closed apartment, may be allowed to continue its work undisturbed until the disinfection is completed.*

The intense activity of formaldehyde as an irritant greatly interferes with its use upon the human body. The application to an ulcerated surface of even its one per cent. solution causes intense pain lasting for a considerable length of time. Nevertheless, formaldehyde is employed to a considerable extent by practical surgeons in cases of *tubercular abscesses*, *infected wounds*, and *infectious inflammations of the mucous membranes*. In many instances it is better to apply a strong solution once or twice than to use a weaker solution more frequently, although a one to five per cent. solution is spoken of by various surgeons as singularly effective. By the previous application of cocaine the pain normally produced by the formaldehyde may be prevented, and there is no danger of systemic poisoning by even the strongest solution. The two per cent. solution of formaldehyde is very effective for the disinfecting of the hands of the surgeon, but has been found too irritating to be practical. A one to two per cent. solution is sometimes employed for the rendering of instruments aseptic, but its use is usually less convenient than that of a simple chamber in which by means of heated paraform the instruments may be disinfected. It is stated that by the employment of this apparatus instruments contained in a chamber one cubic foot square may be absolutely disinfected in fifteen minutes by the evaporation of five grains of paraform at a cost of one cent.

PARAFORM, or *polymerized formaldehyde*, is a colorless, crystalline powder, insoluble in water, of very stable constitution, which when heated slowly gives off formaldehyde gas.

Although it was at first supposed that formaldehyde afforded an almost ideal substance for the preservation of pathological material, experience has shown that its usefulness is lessened by grave difficulties. The injection of the cadaver with the one per cent. solution usually suffices for preservation, and the injected body may be kept indefinitely in a solution of formaldehyde, provided it be not allowed to float upon the top and become mouldy. The emanations from such a cadaver are, however, very irritant, not only to the hands, but also to the respiratory

* There are a number of these lamps upon the market, but according to Edward H. Squibb, Jr., the simplest and cheapest is that originally devised by Sidney Rauschenberg for the New York hospitals. For recent information and discussion, see Squibb's *Ephemeris*, January, 1900.

mucous membrane of the dissector, and the great rigidity produced in the body by the formaldehyde often interferes with the employment of the cadaver for purposes of demonstration.

Kaiserling's Solution is highly recommended for the preservation of pathological specimens without change of color, provided the specimen in the solution be stored in the dark, as very few pigments resist the chemical influence of the sun-rays in a moist vehicle. The microscopic structure of the specimen is said to remain indefinitely unaltered. The solution and method of using are as follows: formaldehyde (forty per cent.), seven hundred and fifty cubic centimetres; distilled water, one thousand cubic centimetres; potassium nitrate, ten grammes; potassium acetate, thirty grammes. The heart, kidney, and brain are kept during a period of twenty-four hours in Kaiserling's fluid, though no harm is done if they remain thirty-six to forty-eight hours. The specimen is then transferred to alcohol of eighty per cent., where it should remain for not longer than twelve hours. Subsequently it is to be put in alcohol of ninety-five per cent. for two hours, and finally preserved in a mixture of equal parts of water and glycerin, to which thirty parts of potassium acetate have been added.

According to Orth,[17] the addition of ten parts of a forty per cent. formaldehyde solution to one hundred parts of Müller's solution greatly increases the preserving and hardening action of that solution. As, however, the compound solution begins to decompose in two days after its mixing, it must be freshly made at the time of using.

In minute quantities (1 to 25,000 or 50,000) formaldehyde has been used for the purpose of preserving milk. In this proportion it does not alter the taste of the milk, and probably does not affect it in any way sufficiently to injure persons of good digestion. It has been shown, however, by A. G. R. Foulerton that the milk is made more indigestible, and in the case of infants the matter might be serious.*

For the destruction of germs in or upon the human body a large number of substances are employed by surgeons. The germicidal power of many of these is slight and often subordinate to other physiological activities, so that they have been considered under different headings in previous chapters of this treatise. The substances still to be spoken of here are readily divided into two sorts: those which not only act as germicides but also destroy organic tissue, and those which are simply germicidal. Of substances, however, which unite germicidal with destructive properties only two recognized by the Pharmacopœia are employed by the practical surgeon,—namely, potassium permanganate and hydrogen dioxide.

POTASSII PERMANGANAS—POTASSIUM PERMANGANATE. U. S.

This salt occurs in slender, prismatic crystals of a dark purple color, inodorous, of a sweetish, disagreeable taste, and forming with water a solution varying from a purplish black to a beautiful reddish lilac, according to the strength. When kept dry, and not exposed to the atmosphere, potassium permanganate is a permanent salt, but whenever in solution it

* See *Lancet*, 1899, ii.; also Bliss and Novy (*Journal of Experim. Med.*, iv.).

is brought into contact with an organic body it at once gives up its oxygen to the latter and is converted into potassa and black manganese oxide.

The destructive power of this salt is beyond question ; but at the same time this power is very limited, as the remedy yields up its own oxygen and becomes inert. According to the experiments of George M. Sternberg,[18] as a germicide the permanganate is potent, 0.12 per cent. (1 part in 833) killing the micrococci of pus in two hours. It affords a very elegant disinfectant and germicidal wash for *wounds*, *ulcers*, *abscesses*, *fetid ozæna*, *otorrhœa*, *leucorrhœa*, etc. In dilute solution its local influence is stimulant and beneficial. When employed in the form of powder it even affects living tissues, acting as a mild caustic, and, as such, may often be applied with advantage to *sloughing ulcers*. As a wash, the strength may vary, according to circumstances, from one to twenty grains to the ounce. The injection of a strong solution of potassium permanganate in the immediate neighborhood of venomous bites is said to be very effective.* The action of the permanganate in these cases is that of a destructive oxidizant.

In a series of laboratory experiments we have determined that potassium permanganate is capable of destroying many and probably all alkaloids, acting very rapidly upon cocaine and morphine, but slowly upon strychnine. We have also found that, as first pointed out by William Moor,[19] administered shortly after the alkaloid it is of practical value in morphine-poisoning. These results are in accordance with those obtained by other experimenters, and with numerous recorded cases of opium-poisoning. The allegation that the permanganate is capable of following and neutralizing the poison in the blood is extremely improbable, and we have found that the hypodermic injection of the permanganate in the lower animals does no good whatever in morphine-poisoning. Indeed, when the permanganate has been used freely, by its local effects it has invariably hastened the death of the animal. Neither do the reports of human poisoning sustain the value of the permanganate given hypodermically in morphine-poisoning. The permanganate should be given in small doses by the mouth at intervals during the acute stage of opium-poisoning, as it has been shown that there is a continuous excretion of morphine from the walls of the stomach, which is subsequently reabsorbed either from the stomach or intestines.

AQUA HYDROGENII DIOXIDI. U. S.—*Solution of Hydrogen Dioxide* (*Solution of Hydrogen Peroxide*).—This is a colorless, odorless, slightly acid, aqueous solution of Hydrogen Dioxide ($H_2O_2 = 33.92$), containing, when freshly prepared, about three per cent., by weight, of the pure dioxide, corresponding to about ten volumes of available oxygen. It was discovered by Thénard in 1818. It consists of water, to a portion of which, by the presenting to it of oxygen in a nascent state, an additional atom

* For cases, see *Texas Courier-Record*, 1888-89, vi.

of this element has combined with the hydrogen, forming the dioxide, $(HO)_2$, or H_2O_2; a small amount of free acid is always left in it as a preservative. It is apt to undergo decomposition, and should be kept in a cool place, and not too tightly stoppered, particularly in hot weather, lest there should be such a brisk evolution of oxygen in a confined space as to cause an explosion. Hydrogen dioxide has been employed to a considerable extent in the arts for bleaching and cleansing human hair, engravings, very fine textile fabrics, etc.

THERAPEUTICS.—The original statement of B. W. Richardson, that hydrogen dioxide is a powerful oxidizant of organic matters, is undoubtedly correct. It is an active coagulant of albumin, and when brought in contact with mucous membranes or ulcerated surfaces evolves gas, at the same time forming a dense white coating. With pus it effervesces very actively, and rapidly destroys the corpuscles, which immediately become granular, lose their shape, and break up into detritus. It is also a powerful deodorant, quickly oxidizing hydrogen sulphide and similar gases. Further, it is a very powerful germicide.

It has been experimentally shown by Pane[20] that (1) Hydrogen peroxide in a solution of 1 to 100 has an energetic germicidal power. (2) The solution 1 to 1000 is a weak antiseptic, and inferior to the corresponding solution of corrosive sublimate. The solution of H_2O_2, in nutritive substances, 1 to 352, not only impedes the development, but after some days kills the spores of the bacillus of charbon. (3) The solution of H_2O_2, in nutritive substances, from 1 to 352 to 5052, impedes the development of the spores of the bacilli of charbon, but does not deprive them of their germinating power when they are transferred to another nutritive substance. Thus, oxygenated water in nutritive substances has a more powerful action on the spores of the bacillus of charbon than has corrosive sublimate, since the spores can develop freely in a solution of gelatin of 1 to 1000 of the mercurial; a conclusion which has been confirmed by Miguet and others.

The cost of hydrogen dioxide is entirely too great to permit the use of it as a general antiseptic, or, as has been proposed, for the purification of water. On the other hand, for some of the purposes of the surgeon it is invaluable, its liquid form making it especially adapted to the cleansing and disinfection of *putrid cavities*, deep infected *wounds*, *abscesses*, etc. Its influence is always immediate and fugacious, so that it cannot replace other antiseptics for the permanent dressing of wounds. Theoretically, it is capable of being used for the disinfecting of hands and instruments.

As a local application in specific *inflammations of mucous membranes* hydrogen peroxide is of the greatest value. In *scarlet fever* and *diphtheria* the official solution may be applied by mop to the pharynx, often with extraordinarily good results. Diluted one-half, it may be injected into the nasal cavities when they are affected. Injection of a solution of from twenty per cent. to full strength has received commendation in the treat-

ment of *gonorrhœa* and *chancre*. The official solution has also been used with alleged great success as a local styptic. As a local application to mucous membranes, the official solution may be used ; the stronger solutions are sometimes too irritating.

As an internal remedy, hydrogen dioxide was strongly recommended by John Day in *diabetes*, *low fever*, and other *typhoid* conditions. On account of its non-absorbability, however, it is of no value in these or any other diseases.

In H. C. Wood's experiments hydrogen dioxide was found, when injected intravenously, to produce immediate wide-spread coagulation of the blood ; and put into the stomach in solution it must destroy itself by acting upon the organic contents and secretions. It is certain that death has been caused both in the lower animals and in man by injecting the solution into the pleural or peritoneal cavity. It has seemed to us probable that these deaths were due to shock, the outcome of the intense local irritation of the pleura or peritoneum, but the cases reported by E. G. Janeway suggest that they have been caused by embolic arrest of circulation in the nerve-centres.

In the case reported by Laach,[21] six injections into the pleural cavity, each containing 0.8 cubic centimetre of a three per cent. solution of hydrogen peroxide, were administered, but at the seventh the patient complained of faintness, the pulse failed, respiration became oppressed, and death occurred in ten minutes. In E. G. Janeway's case collapse with temporary hemiplegia followed immediately upon the injection of hydrogen peroxide into a sacculated empyema. It must be remembered, however, that there are on record a number of cases in which injection of simple water into the pleura has produced collapse, paralysis, or convulsions ; so that it appears doubtful whether, after all, the hydrogen peroxide itself and not the fluid containing it has been the cause of the symptoms in the case just alluded to. On the other hand, probability is lent to the theory that the symptoms above spoken of are due to emboli by the statements of Colasanti and Brugnola,[22] that hypodermic injections of the dioxide rapidly kill the rabbit by causing general gaseous oxygen-emboli ; that in the dog they produce a local emphysema, followed by convulsions, urobilinuria, and other disturbances.

The purely germicidal drugs used about the body which have not hitherto been discussed in this work are as follows :

NAPHTALINUM—NAPHTALIN. U.S.

Naphtalin is a hydrocarbon obtained by the fractional distillation of coal-tar, or sometimes by the dry distillation of organic bodies. It is a white, shining, crystalline substance, fusible at 176° F., insoluble in water, but soluble in alcohol, chloroform, and ether. It is poisonous to the lower forms of life, and under the name of *tar camphor* it has largely supplanted true camphor as a means of preventing the deposition by moths of eggs in woollen clothing, and the destruction by insects in natural history museums, etc. In internal medicine it was some years ago brought forward by Dupasquier as an expectorant especially valuable in *chronic bronchitis* with a large amount of secretion. It has also been

used with asserted excellent results as a *tæniacide*, and as a vermifuge in cases of *seat-worms*, when it should be given by injection, from fifteen grains to half a drachm in two or three ounces of olive oil. First employed by Rossbach, of Jena, in *intestinal catarrh*, it has been largely given in all forms of *intestinal inflammation* and in *typhoid fever*. It has also been used externally as an antiseptic dressing, and as a local application in various skin diseases. It has certainly proved effective in many cases, but has been supplanted by naphtol, which is similar to it in action and probably more effective. The ordinary dose is from two to eight grains (0.13–0.5 Gm.), but as much as eighty grains (5.5 Gm.) per day are said to have been given with good results.* It is best administered as a powder in capsules.

NAPHTOL—NAPHTOL. U.S. (BETA-NAPHTOL.)

Naphtol is a phenol which is present in small quantities in coal-tar, but is usually prepared artificially by heating naphtalin with sulphuric acid and fusing the resulting naphtalin-sulphonic acids with alkaline hydrates. There are two naphtols, alpha and beta, of which beta-naphtol is official. It occurs as colorless or pale buff crystalline laminæ, or as a white or yellowish-white crystalline powder, of a pungent but not persistent taste, and a faint odor suggesting carbolic acid. It is permanent in the air, very slightly soluble in water, very freely soluble in alcohol.

THERAPEUTICS.—Beta-naphtol was introduced by Bouchard and Maximovitch into practical medicine as a germicide which might be used on or within the human body for the purpose of inhibiting the growth of disease-germs. It appears to be of only second rank as a germicide, but to have value on account of being nearly free from toxic powers in relation to the higher animals.

Experimenters are somewhat at variance in regard to the exact germicidal power of beta-naphtol. According to Bouchard and Maximovitch, in the laboratory 1 to 3000 will kill some pathogenetic germs and greatly retard the growth of the bacilli of typhoid fever and of tuberculosis, whilst about three grains per quart will arrest putrefaction. The experiments of Surveyor and Harley,[23] however, indicate that naphtol is less active as a germicide than is bismuth subnitrate. Bouchard and Maximovitch, in contrasting experiments, found that mercuric iodide is six times more antiseptic than beta-naphtol, but that carbolic acid is five times less antiseptic, and creosote four times less antiseptic. The toxic dose of beta-naphtol was found to be 3.8 grains per kilo of the animal, making it two hundred and fifty-three times less poisonous than mercuric iodide. At this rate the poisonous dose for an ordinary man would be between three and four thousand grains. In the animals killed by it, death took place through an arrest of respiration, the heart retaining its activity.

In experiments made to determine whether digestion would be seriously interfered with by beta-naphtol, Clarke found that it has a very

* For a case in which eight grains of pure naphtalin are affirmed to have caused violent gastro-enteritis and nephritis, see *Medical Record*, 1898, liii. 641.

distinct retarding influence on the artificial digestion of egg albumin by peptic fluids, a very slight effect on the artificial digestion of milk by the same, and no effect at all on pancreatic digestion of milk or albumin, nor on the conversion of starch into sugar.

Externally, beta-naphtol was first used in 1881 by Kaposi, of Vienna, who found it to be, when in solution in oil or alcohol, markedly irritating to the skin, 1 part to 100 distinctly affecting *eczematous eruptions*, and 1 to 1½ parts per 100 being sufficient to provoke urticaria on a healthy skin. In the form of soap, containing 2 parts per 100, Kaposi found it useful in *prurigo*, *ichthyosis*, *herpes*, and *favus*, obtaining in many cases the best results by alternating this soap with a sulphur soap, and avoiding in this way a cumulation in the system which he believed was possible by the absorption of the drug. The practice of Kaposi was followed by numerous dermatologists with success, and led to the use of the remedy locally in inflammation of the mucous membranes, such as *conjunctivitis*, *chronic laryngitis*, *otitis*, etc.

Bouchard introduced the internal use of the drug for the purposes of disinfecting pathological cavities, and for intestinal antisepsis, especially in typhoid fever. Following Bouchard, a large number of clinicians have reported excellent results from the administration of the drug in *typhoid fever;* it is affirmed that it lessens the diarrhœa and other local abdominal symptoms both in adults and children. The remedy has also come into use in cases of *dilatation of the stomach*, *intestinal dyspepsia*, *diarrhœa*, or *dysentery*, when it is desired to check fermentative changes in the alimentary canal without producing the astringent or sedative effects of bismuth salts. The slow injection into the trachea, drop by drop, during a half-hour, of two hundred to three hundred cubic centimetres of its solution (1 to 1000) is affirmed by Pignol to be a useful procedure in *pneumonia*. Teissier has given it intravenously; others have exhibited it by the mouth in epidemic *influenza* and low fevers for the relief of albuminuria; but these uses of it are of doubtful value. Larger doses than from three to four grains (0.20–0.25 Gm.), given in capsules every two hours, are apt to disturb the stomach.

The following formulæ may be used in making solutions for local use: 1. *Weak solution*, for parts in which mucous membranes are exposed: naphtol, 5 grammes; alcohol at 60° F., 1 litre. 2. *Ordinary solution:* naphtol, 15 grammes; alcohol at 60° F., 1 litre. 3. *Strong solution*, for touching diseased portions of the skin, or septic excoriations: naphtol, 15 to 500 grammes per litre. 4. *Solution for interstitial injections, or closed septic cavities:* naphtol, 5 grammes; alcohol at 90° F., 33 grammes; hot distilled water, to make 100 cubic centimetres; filter, and use warm. A few drops may be injected into *indurated glands* or *abscesses*.

Carbolic Acid, at one time the most used of all the germicides about the human body, is at present comparatively little employed. It is still used, however, in the strength of one-fourth to one per cent., especially in the form of carbolated vaseline, as a local application to wounds. For germicidal power, see page 555.

Homologous with carbolic acid are the three isomeric *cresols*, *ortho-cresol*, *metacresol*, and *paracresol*, whose insolubility long prevented their use as practical germicides, but of which various emulsions have been put upon the market. Of these emulsions the most important is *creolin*, in which the cresol is said to be suspended by means of resin soap. It has been asserted that creolin is not poisonous, Jessner stating that he had given one hundred and twenty grains (7.77 Gm.) to a man without production of distinct symptoms. It is almost certain, however, that its apparent lack of toxicity depends upon its non-absorption, due to insolubility ; and human poisoning has been caused by it.

Bitter[24] has seen restlessness, anxiety, nausea, amblyopia, and a tendency to syncope, with a peculiar strong taste of tea or smoke, produced by the drug. The urine in some of his cases was dark and strongly albuminous, evidently acute nephritis having set in. Fliesburg[25] details a case of a three-weeks'-old babe who was killed by thirty drops of undiluted creolin, the chief symptoms being those of violent irritation of the mouth and upper respiratory and digestive tracts. Death occurred chiefly through inflammation of the glottis.

As a germicidal application, creolin has been used in the strength of from one-fourth to one per cent. solution. Creolin gauze, as usually sold, contains from five to ten per cent. of the creolin. Neudörfer recommends for local application to infected wounds a powder composed of asbestos with twenty per cent. of creolin. Locally applied, creolin has been largely used with great success in the treatment of *scabies*, in the form of a five per cent. ointment with vaseline. In *ammoniacal cystitis*, washing out of the bladder with a half per cent. solution of creolin has yielded excellent results. It also seems to be an effective local application in the treatment of *acute* and *chronic dysentery*, and also in the *cholera morbus of children*. In the case of adults, large enemata of a one-half of one per cent. solution may be used ; in the case of infants, the strength should be about one-half of this. As a local application in *gonorrhœa*, creolin has been employed with alleged excellent results both in the form of bougies containing half a grain of creolin and the injection of creolin dissolved in olive oil (1 in 3). For washing out the uterus after *labor*, the strength of the solution should be one per cent.

Lysol is a brown, oily looking, clear liquid, with a feebly aromatic, creosote-like odor, which is said to contain fifty per cent. of cresols, and to form with water a clear soapy liquid, and to be miscible also with alcohol and glycerin. According to V. Gerlach,[26] it is more powerful as a germicide than is creolin, and yields a one per cent. soapy solution which may be used for the purpose of surgical disinfection of the hands without the addition of soap. Toxicologically, physiologically, and surgically lysol probably is almost identical with creolin, and in sufficient dose it may produce fall of temperature and general depression, with nephritis.

CRESOL SALICYLATE, or *Cresalol*, is affirmed by Nencki to undergo decomposition in the intestines, yielding cresol and salicylic acid. It is said to act very much as does salol, but to be less poisonous on account of the great insolubility of cresol.

ACIDUM BORICUM—BORIC ACID. U. S.

Boric (or *Boracic*) acid crystallizes in white translucent scales, soluble in about thirty parts of cold water, much more soluble in boiling water, which on cooling precipitates all but about twenty-three grains to the fluidounce. Hot glycerin dissolves and holds upon cooling as much as three drachms to the fluidounce. *Borax* (SODII BORAS, U. S.) occurs in white, flattened, prismatic crystals, soluble in twelve times their weight of cold water. A. Dujardin[27] states that borax is incompatible with the alkaloids.

PHYSIOLOGICAL ACTION.—*Local Action.*—Locally, boric acid is, when in concentrated form, distinctly irritant; in dilute solution, stimulant and antiseptic, and having even a soothing influence upon mucous membranes. Its sodium salt even in concentrated form is scarcely irritant. The germicidal power of boric acid and its salts is too feeble to be relied upon in cases of serious infection.

In 1874 Dumas and Schnatzles[28] announced that borax is poisonous to the lower forms of life. In Bucholz's[29] experiments, 0.75 per cent. of boric acid was found sufficient to prevent the development of bacteria. In the experiments of Walb,[30] a two per cent. solution of borax distinctly checked the putrefaction of solution of fibrin; a five per cent. solution kept the solution fresh for nineteen days. Fresh muscle-fibres from oxen were kept fresh many days by a one per cent. solution. Sternberg[31] found that boric acid and sodium biborate are inefficient as germ-destroyers, but have considerable antiseptic power. The experiments of Sternberg have received corroboration from E. Andrews.[32]

Absorption and Elimination.—Boric acid and its soluble salts are rapidly absorbed and rapidly eliminated from the kidneys, escaping also in the perspiration, saliva, and fæces (Johnson).

General Effects.—The physiological action of boric acid and its salts is very feeble. No symptoms are produced by large doses, although according to Max Grüber[33] and to Johnson[34] such doses act as a diuretic, and according to Grüber increase the elimination of urea. In poisoning by the acid the symptoms have varied somewhat, but in most if not all the cases there have been great depression of spirits, fall of bodily temperature, a very feeble pulse,—rapid or slow,—and an erythematous eruption accompanied by much swelling of the parts, and especially affecting the lower extremities and followed by exfoliation; nausea, violent vomiting, and hiccough have been present in some cases; ecchymoses have been noted; the mind usually remains clear until late in the poisoning, but

death has been preceded by coma, with disturbances of the respiration and involuntary discharges.*

The question as to the effect of the continuous administration of borax is of importance, in view of its use as a preservative of food and as a continuous remedy in epilepsy. That such use of the drug may be harmful is indicated by the experiments of H. E. Annett,[35] who found that five kittens fed on milk containing eighty grains of boric acid to the gallon all died during the fourth week. Any deleterious effects produced by these continuing doses are probably due to nephritis, since Jacob Plaut[36] has shown that the acid may produce acute parenchymatous nephritis. Moreover, Ch. Féré[37] has noticed in the long-continued use of borax in epilepsy marked irritation of the kidneys, with albuminuria, ending in one or two cases in uræmia and death.†

In experiments made by H. C. Wood and E. T. Stewart, enormous doses were required to affect the frog ; they depressed the spinal centres and produced progressive loss of voluntary and reflex activity without affecting nerve or muscle.‡ A saturated solution of sodium quadroborate brought in direct contact with the heart exercised a very feeble depressant influence, and when injected in sufficient amount into the jugular vein of the mammal lowered the arterial pressure.

THERAPEUTICS.—As originally suggested by Rosenthal,[38] boric acid has been found to be an efficient remedy in *cystitis* with ammoniacal urine, rendering the urine acid probably by checking the fermentation. In our own practice great relief has been obtained in the *cystitis of spinal diseases* by washing out the bladder with a few ounces of a saturated solution of boric acid after the use of the catheter. The acid may be given in doses of ten grains (0.6 Gm.) three to six times a day ; the salt, twenty grains to a drachm (1.3–4 Gm.) : in each case administered in diluted watery solution. As a disinfectant and soothing eye-wash its solution is much used in *conjunctivitis*. The strength may vary from five grains to the ounce up to saturation. Boric acid is also employed as an

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* Cases : George T. Welch (*New York Med. Rec.*, 1888, xxxiv.), two ounces of boric acid in the vagina,—recovery ; Mododewkow (*St. Louis Clin. Rec.*, 1881), death from washing out internal cavities with five per cent. solution ; Hogner (*Schmidt's Jahrb.*, ccii. 238), death from washing the stomach with two and a half per cent. solution (see also *Med. News*, xl. 704). There is no reason for believing that boric acid had anything to do with the symptoms in the case of alleged poisoning reported in *Med. News*, xliii. 199.

† G. Lemoine reports (*Bull. Gén. Thérap.*, May, 1892) a bluish-gray line, like that of lead-poisoning, as present upon the gums in cases of epilepsy in which borax had been given very freely and continuously. Cyon (*Hoffmann und Schwalbe's Jahresb.*, 1879, 301) asserts that daily doses of three drachms of borax increase the appetite and digestion in dogs without causing other effect, unless it be gain in weight.

‡ A very curious effect is said (Schiff, *Rev. Méd. de Suisse Rom.*, 1881, 244) to be produced by the local application of boric acid to nerves : the part affected is affirmed to lose its power of originating but not of transmitting impulses, so that if the galvanic current be applied to the part of the nerve which has been exposed to the drug no muscular contractions result, but if the poles be placed above this part the distal muscles respond at once.

antiseptic dressing to fresh *wounds*, *abscesses*, old *burns*, etc. (See especially M. Greene.[39])

Wounds dressed in a dry manner with a lint made by saturating ordinary patent lint with a saturated solution of boric acid, and drying, are stated to heal as rapidly as when a complicated antisepsis is employed. Greene prepares an ointment by melting one part each of spermaceti and white wax with six parts of vaseline, and adding, while hot, two to four parts of a saturated glycerite of boric acid.

The saturated solution of boric acid has been especially recommended in phlegmonous *erysipelas*.* Both boric acid and borax are of excellent service in *aphthous ulceration*, *diphtheria*, and other *inflammations of the mouth*, in which crystals of the salt may be allowed slowly to dissolve in the mouth. C. F. Folsom[40] has strongly recommended borax in the dose of fifteen grains three times a day in *epilepsy*. We have tried the remedy carefully in a large number of cases, increasing the dose until pronounced gastro-intestinal irritation was caused, without affecting perceptibly the return or severity of the paroxysms.

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* See *Lancet*, May, 1873; May, 1876; also F. L. Lebovicz (*Gaz. Hebdom. de Méd.*, 1884, xxi. 624).

APPENDIX.

APOTHECARIES' WEIGHT—APOTHECARIES' MEASURE.

FORMERLY OFFICIAL IN THE UNITED STATES PHARMACOPŒIA.

Pound,	℔	=	12 Ounces.	Gallon,	C	=	8 Pints.
Ounce,	℥	=	8 Drachms.	Pint,	O	=	16 Fluidounces
Drachm,	ʒ	=	3 Scruples.	Fluidounce,	f℥	=	8 Fluidrachms.
Scruple,	℈	=	20 Grains.	Fluidrachm,	fʒ	=	60 Minims.
Grain,	gr.	=	1 Grain.	Minim,	♏	=	1 Minim.

WEIGHTS AND MEASURES OF THE METRICAL OR FRENCH SYSTEM.

NOW OFFICIAL IN THE UNITED STATES PHARMACOPŒIA.

MEASURES OF LENGTH.

One Myriametre	=	10,000 Metres.
One Kilometre	=	1,000 Metres.
One Hectometre	=	100 Metres.
One Decametre	=	10 Metres.
One METRE	=	the ten-millionth part of a quarter of the meridian of the earth.
One Decimetre	=	the tenth part of one Metre, or 0.1 Metre.
One Centimetre	=	the hundredth part of one Metre, or 0.01 Metre; written Cm.
One Millimetre	=	the thousandth part of one Metre, or 0.001 Metre; written Mm.

WEIGHTS.

One Myriagramme	=	10,000 Grammes.
One Kilogramme	=	1,000 Grammes.
One Hectogramme	=	100 Grammes.
One Decagramme	=	10 Grammes.
One GRAMME	=	the weight of a cubic Centimetre of Water at 4° C.; written Gm.
One Decigramme	=	the tenth part of one Gramme, or 0.1 Gramme.
One Centigramme	=	the hundredth part of one Gramme, or 0.01 Gramme.
One Milligramme	=	the thousandth part of one Gramme, or 0.001 Gramme.

MEASURES OF CAPACITY.

One Myrialitre	=	10 cubic Metres, or the measure of 10 Milliers of Water.
One Kilolitre	=	1 cubic Metre, or the measure of 1 Millier of Water.
One Hectolitre	=	100 cubic Decimetres, or the measure of 1 Quintal of Water.
One Decalitre	=	10 cubic Decimetres, or the measure of 1 Myriagramme of Water.
One LITRE	=	1 cubic Decimetre, or the measure of 1 Kilogramme of Water.
One Decilitre	=	100 cubic Centimetres, or the measure of 1 Hectogramme of Water.
One Centilitre	=	10 cubic Centimetres, or the measure of 1 Decagramme of Water.
One Millitre	=	1 cubic Centimetre, or the measure of 1 Gramme of Water.

RELATION OF APOTHECARIES' WEIGHTS AND MEASURES TO EACH OTHER.

In distilled water at the temperature of 60°.

One Pound	=	0.7900031 Pint	=	6067.2238 Minims
One Ounce	=	1.0533376 Fluidounces	=	505.6019 Minims
One Drachm	=	1.0533376 Fluidrachms	=	63.2002 Minims
One Scruple	=	. . . . .	=	21.0667 Minims
One Grain	=	. . . . .	=	1.0533 Minims
One Gallon	=	10.1265427 Pounds	=	58328.8862 Grains
One Pint	=	1.2658178 Pounds	=	7291.1107 Grains.
One Fluidounce	=	0.9493633 Ounce	=	455.6944 Grains.
One Fluidrachm	=	0.9493633 Drachm	=	56.9618 Grains.
One Minim		. . . . .	=	0.9493 Grain.

RELATION OF APOTHECARIES' OR WINE MEASURE TO CUBIC MEASURE.

One Gallon	=	231.	Cubic Inches.	One Fluidrachm	=	0.22558	Cubic Inch
One Pint	=	28.875	Cubic Inches.	One Minim	=	0.00375	Cubic Inch
One Fluidounce	=	1.80468	Cubic Inches.				

RELATION OF APOTHECARIES' WEIGHTS TO METRICAL WEIGHTS.

Fractions of a grain in Milligrammes.

Grain.		Milligrammes.
1/64	=	1.012
1/60	=	1.079
1/50	=	1.295
1/48	=	1.349
1/40	=	1.619
1/36	=	1.799
1/30	=	2.159
1/25	=	2.591
1/24	=	2.699
1/20	=	3.239
1/15	=	4.049
1/15	=	4.319
1/12	=	5.399
1/10	=	6.479
1/8	=	8.098
1/6	=	10.798
1/5	=	12.958
1/4	=	16.197
1/3	=	21.597
1/2	=	32.395

Grains in equivalent metrical weights.

Grains.		Centigrammes.
1	=	6.479
		Decigrammes.
2	=	1.295
3	=	1.943
4	=	2.591
5	=	3.239
6	=	3.887
7	=	4.535
8	=	5.183
9	=	5.831
10	=	6.479
12	=	7.775
15	=	9.718
		Grammes.
16	=	1.036
20	=	1.295
24	=	1.555
25	=	1.619
30	=	1.943
40	=	2.591
50	=	3.239
60	=	3.887

Drachms, Ounces, and Pounds in equivalent metrical weights.

Drachms.		Grammes.
1	=	3.887
2	=	7.775
		Decagrammes.
3	=	1.166
4	=	1.555
5	=	1.943
6	=	2.332
7	=	2.721
Ounces.		
1	=	3.1103
2	=	6.2206
3	=	9.3309
		Hectogrammes.
4	=	1.2441
5	=	1.5551
6	=	1.8661
7	=	2.1772
8	=	2.4882
9	=	2.7992
10	=	3.1103
11	=	3.4213
Pounds.		
1	=	3.7324
2	=	7.4648
		Kilogrammes.
3	=	1.1197

RELATION OF METRICAL WEIGHTS TO APOTHECARIES' WEIGHTS.

Metrical Weights.		*Exact equivalents in grains.*	*Approximate equivalents in grains.*
Milligrammes.			
1	=	.0154	$\frac{1}{65}$
2	=	.0308	$\frac{1}{32}$
3	=	.0463	$\frac{1}{22}$
4	=	.0617	$\frac{1}{16}$
5	=	.0771	$\frac{1}{13}$
6	=	.0926	$\frac{1}{11}$
7	=	.1080	$\frac{1}{9}$
8	=	.1234	$\frac{1}{8}$
9	=	.1389	$\frac{1}{7}$
Centigrammes.			
1	=	.1543	$\frac{1}{6}$
2	=	.3086	$\frac{1}{3}$
3	=	.4630	$\frac{5}{11}$
4	=	.6173	$\frac{7}{11}$
5	=	.7717	$\frac{3}{4}$
6	=	.9260	$\frac{15}{16}$
7	=	1.0803	1
8	=	1.2347	1¼
9	=	1.3890	1⅓
Decigrammes.			
1	=	1.543	1½
2	=	3.086	3
3	=	4.630	4½
4	=	6.173	6
5	=	7.717	7½
6	=	9.260	9
7	=	10.803	11
8	=	12.347	12½
9	=	13.890	14

Metrical Weights.		*Exact equivalents in grains.*	*Approximate equivalents in Troy Weight.*
Grammes.			
1	=	15.434	gr. xv.
2	=	30.868	℥ss.
3	=	46.302	℈ij.
4	=	61.736	℥i.
5	=	77.170	℈iv.
6	=	92.604	℥iss.
7	=	108.038	℈vss.
8	=	123.472	℥ij.
9	=	138.906	℈vij.
Decagrammes.			
1	=	154.340	℥iiss.
2	=	308.680	℥v.
3	=	463.020	℥viiss.
4	=	617.360	℥x.
5	=	771.701	℥xiij.
6	=	926.041	℥xv.
7	=	1,080.381	℥xviij.
8	=	1,234.721	℥xx.
9	=	1,389.062	℥xxiij.
Hectogrammes.			
1	=	1,543.402	℔iii ℈v.
2	=	3,086.804	℔vj ℥iij.
3	=	4,630.206	℔ix ℥v.
4	=	6,173.609	℔i ℥vij.
5	=	7,717,011	℔i ℔iv.
6	=	9,260.413	℔i ℔vij.
7	=	10,803.816	℔i ℔x ℥iv
8	=	12,347.218	℔ij ℔i ℥v
9	=	13,890.620	℔ij ℔v.
Kilogramme.			
1	=	15,434.023	℔ij ℔vij.
Myriagramme.			
1	=	154,340.23	℔ xxvi ℔ix ℥iv.

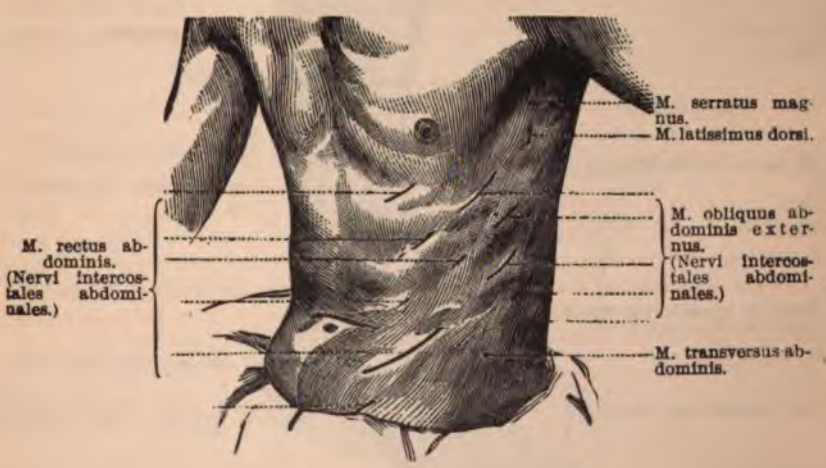
TABLE OF THE PROPORTION BY MEASURE OF ALCOHOL (SP. GR. 0.825) CONTAINED IN ONE HUNDRED PARTS OF DIFFERENT WINES, ETC.*

Lisa (mean)	25.41	Teneriffe (C.)	16.61	Lunel	15.52
Raisin wine (mean)	25.12	Colares	19.75	Ditto (F.)	18.10
Marsala [Sicily madeira] (mean)	25.09	Lachryma Christi	19.70	Shiraz	15.52
strongest (J.)	21.10	White Constantia	19.75	Ditto (C.)	15.56
weakest (J.)	19.90	Red Constantia	18.92	Syracuse	15.28
Port, strongest	25.83	Lisbon	18.94	Sauterne	14.22
mean	22.96	Ditto (C.)	19.09	Burgundy (mean)	14.57
weakest	19.00	Bucellas	18.49	strongest (J.)	13.20
strongest (C.)	20.49	Red madeira (mean)	20.35	weakest (J.)	10.10
mean (C.)	18.68	Cape muscat	18.25	Hock (mean)	12.08
weakest (C.)	16.80	Cape madeira (mean)	20.51	strongest (J.)	13.00
strongest (J.)	23.20	Grape wine	18.11	weakest (J.)	9.50
weakest (J.)	20.70	Calcavella (mean)	18.65	Nice	14.63
White port (C.)	17.22	Vidonia	19.25	Barsac	13.86
Madeira, strongest	24.42	Alba flora	17.26	Tent	13.30
mean	22.27	Zante	17.05	Champagne (mean)	12.61
weakest	19.24	Malaga	17.26	Ditto (F.)	12.20
strongest (C.)	20.35	White hermitage	17.43	Ditto, strongest (J.)	14.80
strongest (J.)	19.70	Roussillon (mean)	18.13	weakest (J.)	14.10
weakest (J.)	19.00	Claret (strongest)	17.11	Red hermitage	12.32
Sercial madeira	21.40	mean	15.10	Vin de Grave (mean)	13.37
Ditto (C.)	18.50	weakest	12.91	Frontignac (Rives Altes)	12.79
Sherry, strongest	19.81	ditto (F.)	14.73	Ditto (C.)	12.29
mean	19.17	vin-ordinaire (C.)	10.42	Côte rôtie	12.32
weakest	18.25	Château-Latour, 1825 (C.)	9.38	Tokay	9.88
strongest (C.)	19.31	first growth, 1811 (C.)	9.32	Rudesheimer, first quality (C.)	10.14
mean (C.)	18.47	strongest (J.)	11.10	inferior (C.)	8.35
weakest (C.)	16.96	weakest (J.)	9.10	Hambacher, first qual. (C.)	8.88
Amontillado (C.)	15.18	Malmsey madeira	16.40	Catawba (Stearns)	8 to 11
strongest (J.)	24.70	Ditto (C.)	15.60		
weakest (J.)	15.40				
Teneriffe	19.79				

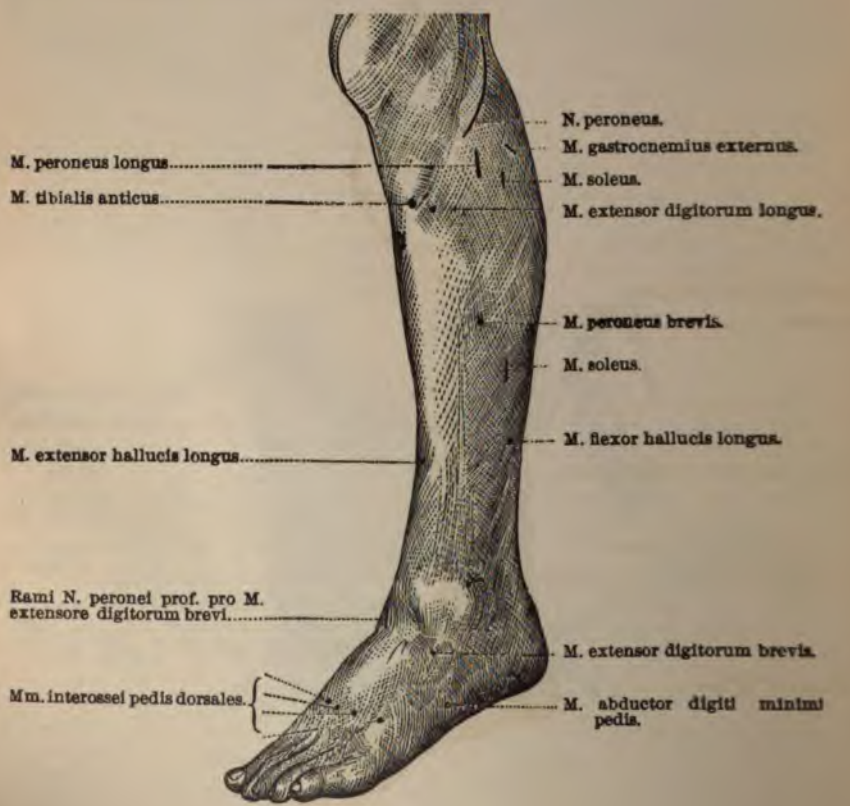
Cider, highest average	9.87	Ale (Edinburgh)	6.20	Brandy	53.39
lowest average	5.21	Ale (Dorchester)	5.56	Rum	53.68
Perry, average of four samples	7.26	Brown stout	6.80	Gin	51.60
Mead	7.32	London porter	4.20	Scotch whisky	54.32
Ale (Burton)	8.88	London small beer	1.28	Irish whisky	53.90

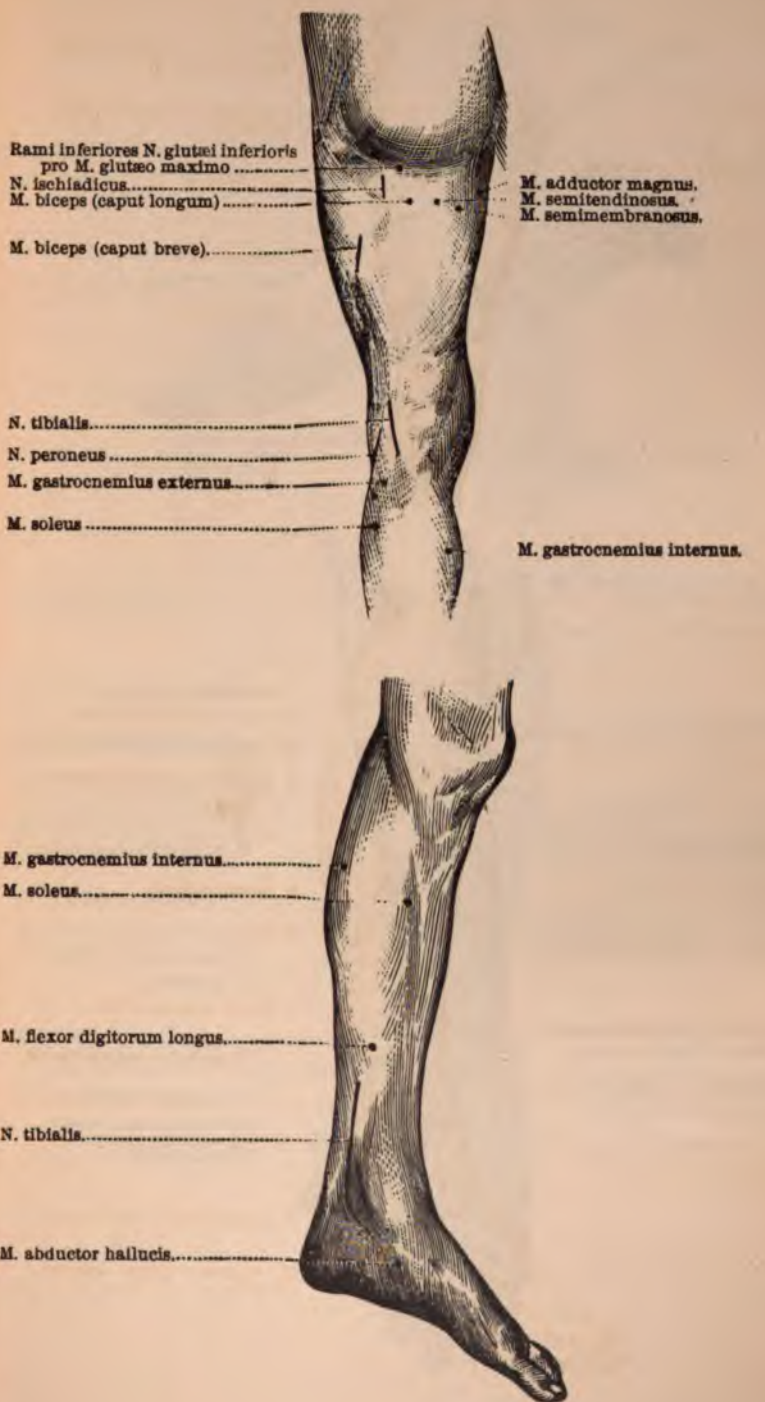
* The analyses whose results are given in this table were mostly made by Mr. Brande. When no mark is attached, the quotation is upon his authority. When the mark (F.) is added, the analysis was made by Julia-Fontenelle; (C.), by Professor Christison; (J.), by Dr H. Bence Jones.

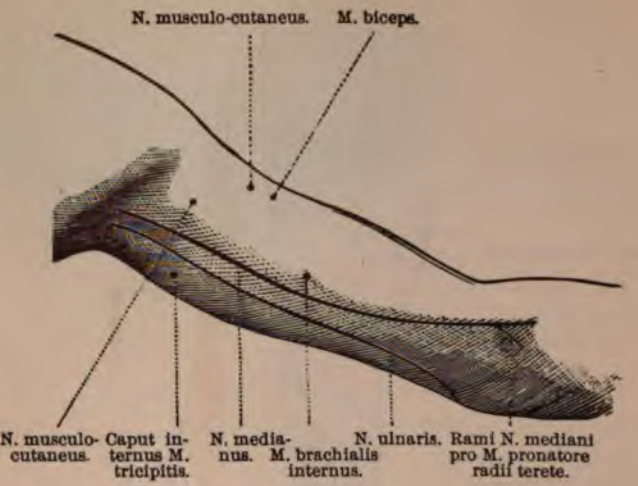
1, M. corrugator supercil.; 2, M. compressor nasi et pyramidal. nasi; 3, M. orbicular. palpebr.; 4, M. levator lab. sup. alæque nasi; 5, M. levator lab. sup. propr.; 6, M. zygomatic. minor; 7, M. dilatat. narium ant. et post.; 8, M. zygomatic. major; 9, M. orbicularis oris; 10, Ram. comm. pro Mm. triangular. et levator menti; 11, M. levator menti; 12, M. quadratus menti; 13, M. triangularis menti; 14, Ram. subcutan. colli N. facial.; 15, Ram. cervical. pro Platysmat.; 16, M. sterno-hyoideus; 17, M. omo-hyoideus; 18, M. sterno-thyroideus; 19, M. sterno-hyoideus; 20, M. frontalis; 21, Mm. attrahens et attollens auriculæ; 22, Mm. retrahens et attoll. auriculæ; 23, M. occipitalis; 24, Nerv. facialis; 25, Ram. auricular. post. prof. N. facialis; 26, M. stylo-hyoideus; 27, M. digastricus; 28, Ram. buccales, N. facialis; 29, M. splenius capitis; 30, Ram. subcutan. maxill. infer.; 31, Ram. ext. N. accessorii Willisii; 32, M. sterno-cleido-mastoideus; 33, M. cucullaris; 34, M. sterno-cleido-mastoideus; 35, M. levator anguli scapulæ; 36, N. thoracic. post. (Mm. rhomboidei); 37, N. phrenicus; 38, M. omohyoid.; 39, N. thoracic. lateral. (M. serrat. magn.); 40, N. axillaris; 41, Ram. plex. brachialis (N. musculo-cutan., pars N. mediani); 42, N. thoracic. ant. (M. pectorales).

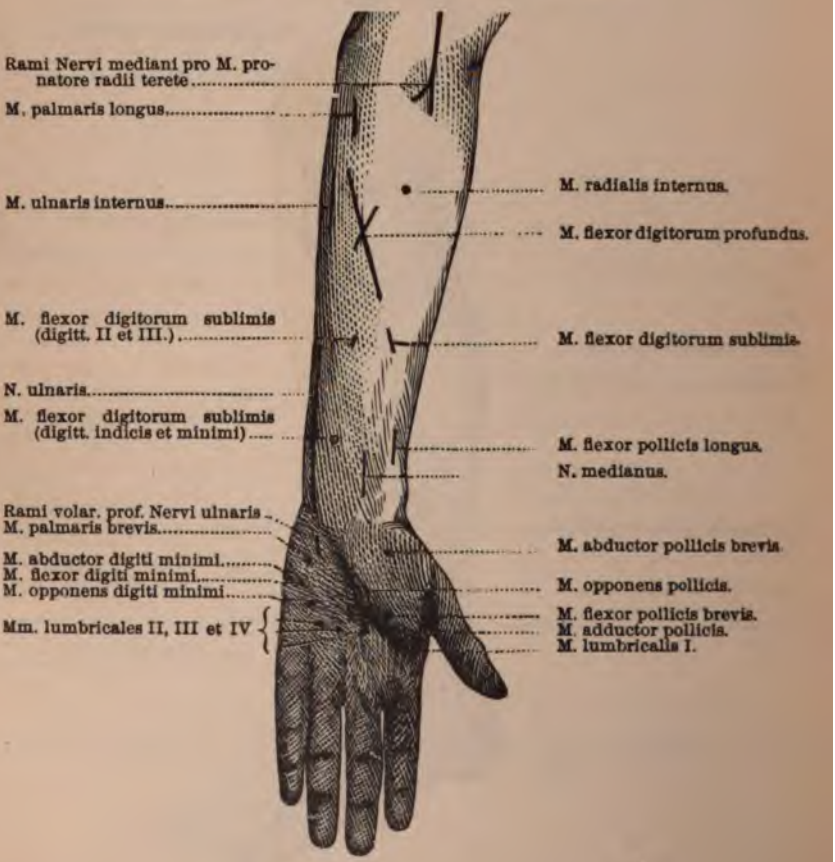


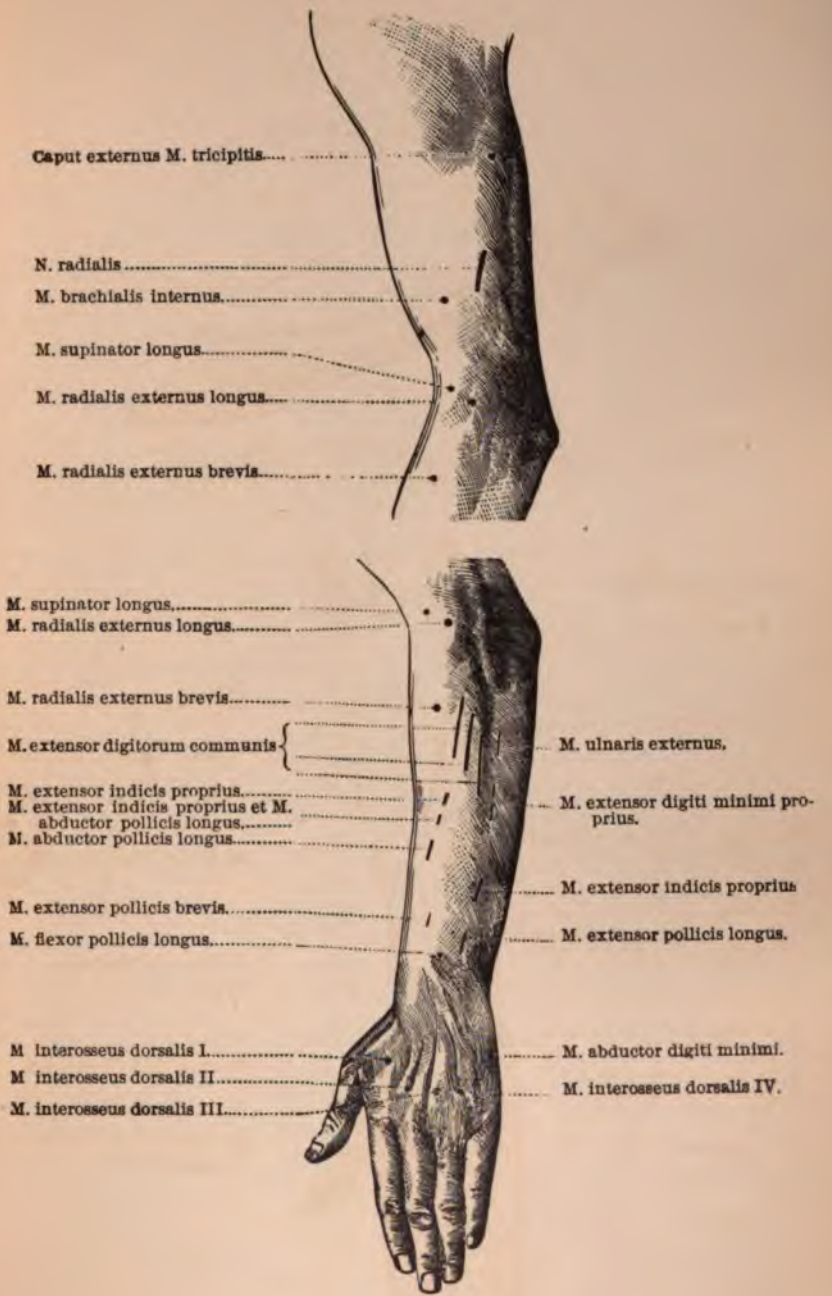
N. cruralis
N. obturatorius
M. sartorius
M. adductor longus
Rami N. cruralis pro M. quadriceps.
M. cruralis
Rami N. cruralis pro M. vasto interno
M. tensor vaginæ femoris. (Rami N. glutæi superioris.)
M. tensor vaginæ femoris. (Rami N. cruralis.)
M. rectus femoris.
M. vastus externus.
M. vastus externus.

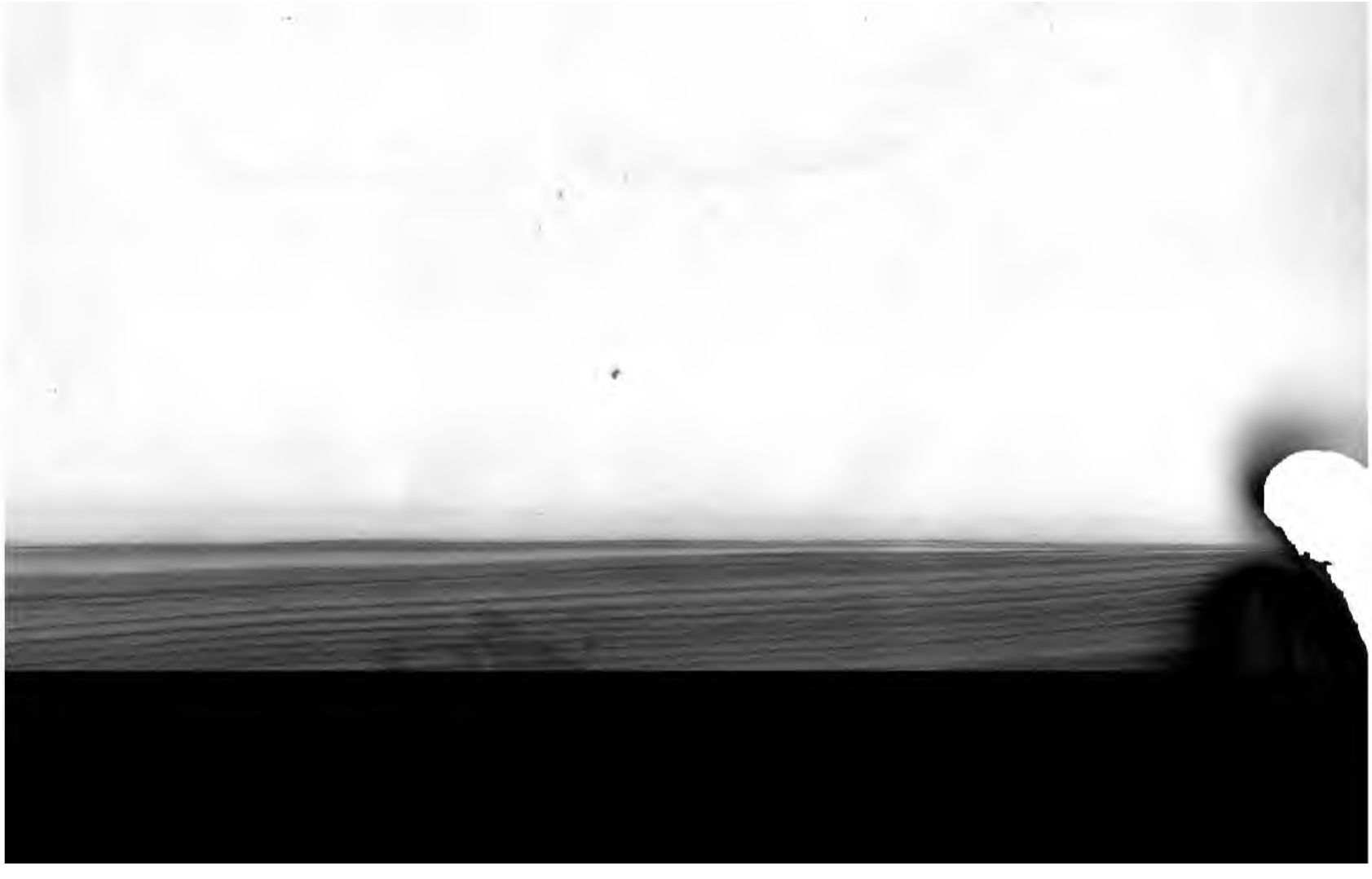

M. peroneus longus
M. tibialis anticus
M. extensor hallucis longus
Rami N. peronei prof. pro M. extensore digitorum brevi
Mm. interossei pedis dorsales
N. peroneus.
M. gastrocnemius externus.
M. soleus.
M. extensor digitorum longus.
M. peroneus brevis.
M. soleus.
M. flexor hallucis longus.
M. extensor digitorum brevis.
M. abductor digiti minimi pedis.


Rami inferiores N. glutæi inferioris pro M. glutæo maximo
N. ischiadicus
M. biceps (caput longum)
M. biceps (caput breve)
N. tibialis
N. peroneus
M. gastrocnemius externus
M. soleus
M. adductor magnus.
M. semitendinosus.
M. semimembranosus.
M. gastrocnemius internus.
M. gastrocnemius internus
M. soleus
M. flexor digitorum longus
N. tibialis
M. abductor hallucis


N. musculo-cutaneus.
M. biceps.
N. musculo-cutaneus.
Caput internus M. tricipitis.
N. medianus.
M. brachialis internus.
N. ulnaris.
Rami N. mediani pro M. pronatore radii terete.


Rami Nervi mediani pro M. pronatore radii terete
M. palmaris longus
M. ulnaris internus
M. flexor digitorum sublimis (digitt. II et III.)
N. ulnaris
M. flexor digitorum sublimis (digitt. indicis et minimi)
Rami volar. prof. Nervi ulnaris
M. palmaris brevis
M. abductor digiti minimi
M. flexor digiti minimi
M. opponens digiti minimi
Mm. lumbricales II, III et IV
M. radialis internus.
M. flexor digitorum profundus.
M. flexor digitorum sublimis.
M. flexor pollicis longus.
N. medianus.
M. abductor pollicis brevis.
M. opponens pollicis.
M. flexor pollicis brevis.
M. adductor pollicis.
M. lumbricalis I.


Caput externus M. tricipitis
N. radialis
M. brachialis internus
M. supinator longus
M. radialis externus longus
M. radialis externus brevis
M. supinator longus
M. radialis externus longus
M. radialis externus brevis
M. extensor digitorum communis
M. extensor indicis proprius
M. extensor indicis proprius et M. abductor pollicis longus
M. abductor pollicis longus
M. extensor pollicis brevis
M. flexor pollicis longus
M. interosseus dorsalis I
M. interosseus dorsalis II
M. interosseus dorsalis III
M. ulnaris externus.
M. extensor digiti minimi proprius.
M. extensor indicis proprius
M. extensor pollicis longus.
M. abductor digiti minimi.
M. interosseus dorsalis IV.



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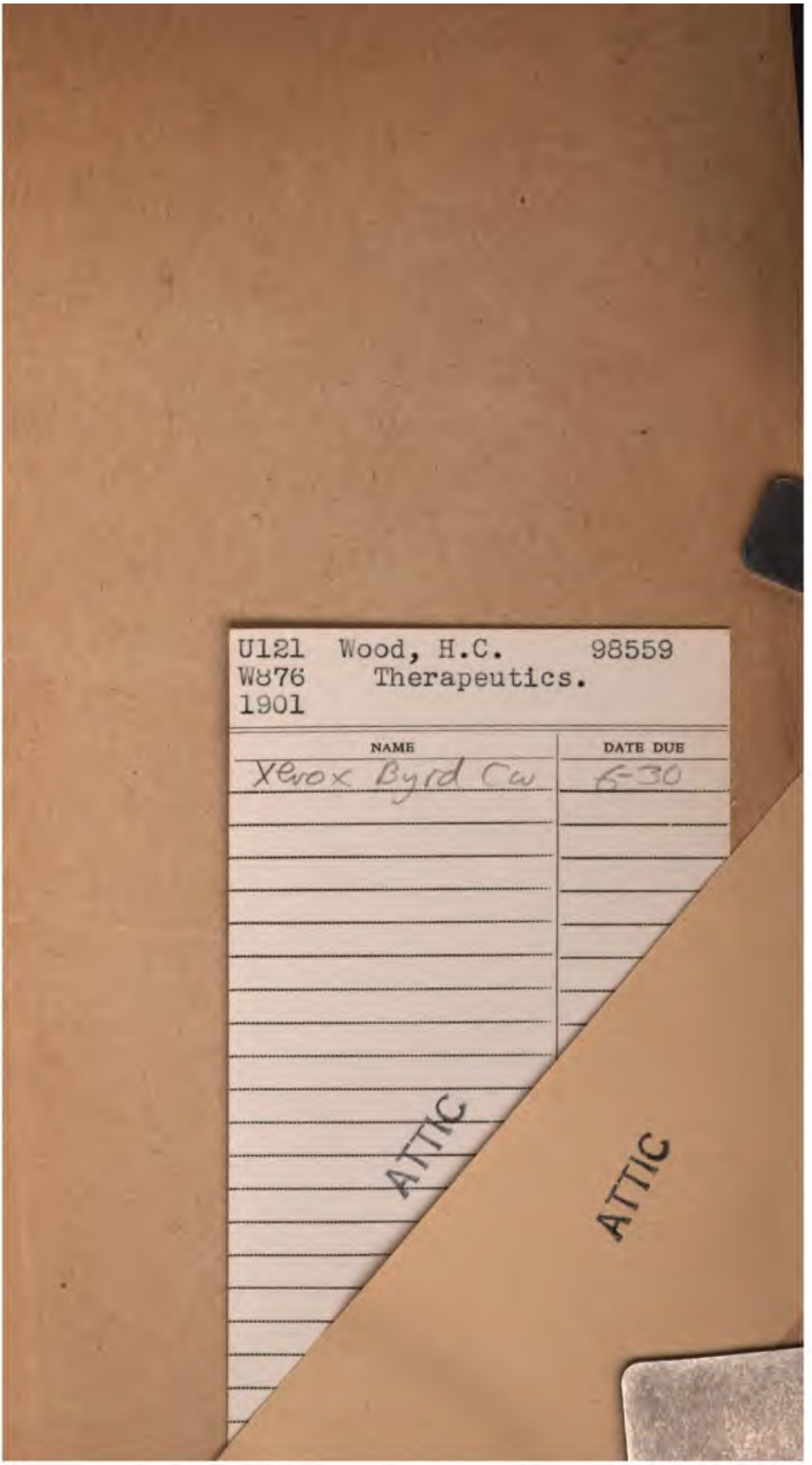
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